



**The role and importance of invasive hemodynamic monitoring
in septic shock and ARDS patients**

Ph.D. thesis

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2014

1. List of abbreviations

CI - cardiac index, **SV** - stroke volume, **HR** - heart rate, **PEEP** – positive end-expiratory pressure, **SvO₂** - venous oxygen saturation, **ScvO₂** – central venous saturation, **VO₂** – oxygen consumption, **DO₂** –oxygen delivery, **ICG** - indocyanine green, **ICG – PDR** - indocyanine green plasma disappearance rate, **PCT** - procalcitonin, **ARDS** - acute respiratory distress syndrome, **ITBV** – intrathoracic blood volume, **EVLW** – extravascular lung water, **NAC** - N-acetyl-cysteine

2. Introduction

Intensive care is one of the most expensive fields in medicine. Therefore it is important that we have therapies and methods which improve patients' outcome. With the development of the technique our possibilities become greater as well; however we have to search a place for the new methods and therapies. We can fulfill this by performing studies, analyzing data and when it is possible having meta-analysis in clinical trials. In my thesis I wrote about studies, where in different patient population I examined the hemodynamic effect of different therapies, or the traditional monitoring method was supplemented by a new method. Patient populations were the following: ARDS-patient, patients with septic shock, patients with liver cancer.

ARDS belongs to the clinical pictures with high mortality. Its pathophysiology and therapy isn't clarified fully yet. One common feature of the treatments of acute lung injury is the "lung protective ventilation" and the "open lung conception". The aim of the "open lung conception" is to recruit alveoli with high airway pressures (lung recruitment) and keep up an optimal positive end-expiratory pressure to keep the alveoli open. The optimal PEEP pressure is a continuously changing target value, what should be titrated individually by each patient. During the lung recruitment applied high intrathoracic pressures can cause hemodynamic instability that is why continuous hemodynamic monitoring is important.

Shock is a complex syndrome, when decreased blood flow leads to cell damage because of hypoxia, and consequently it leads to organ failure. In circulatory failure the balance between tissue oxygen consumption (VO₂) and delivery (DO₂) will be impaired. In the ICU our aim is to ensure the appropriate oxygenation. The optimal oxygen consumption of the body is demonstrated by the SvO₂. Mixed central venous saturation can be an appropriate alternative to SvO₂. ScvO₂ is easy to measure via the central venous line, what is commonly inserted by most of the ICU patients. It can happen through co-oxymetry or through a newly developed fiberoptic catheter (CeVOX, Pulsion) which in contrast measures continuously ScVO₂.

The first line treatment of hypotonia in severe septic shock is aggressive fluid therapy. In case of inadequacy, vasopressor and/or inotropic agent should be applied. The most frequent applied vasopressor is norepinephrine, which is a potent α -agonist with small β -adrenergic effect. The use of norepinephrine is contradictory, because through its vasoconstrictor effect it can worsen the microcirculation in the hepato-splanchnic system. Ischemia can lead to multiple organ failure. In our study we combined dobutamine and norepinephrine, and monitored its effect through indocyanine green excretion.

During liver resection surgeons apply clamping to avoid extreme bleeding. The Pringle maneuver is very often used during liver surgery to minimize blood loss. A large haemostat is used to clamp the hepatoduodenal ligament interrupting the flow of blood through the hepatic artery and the portal vein and thus helping to control bleeding from the liver. However it can directly lead to reperfusion phenomenon in the liver and it has recently been suggested that it should be avoided in hepatectomy for cancer patients due to its side effects on tumor recurrence and worse prognosis. Against the released free radicals scavengers can be used. A potent free radical scavenger is NAC, what replenishes the

endogenous antioxidant system of the cell. However it has been only rarely examined in liver resection. To monitor liver function we can use traditional laboratory methods and the dynamic liver function test (ICG-PDR).

3. Aims/ Hypothesis

1. The aim of our lung recruitment study was to investigate respiratory and hemodynamic changes during the procedure and descending optimal positive end-expiratory pressure (PEEP) titration. We investigated the relationship between PEEP, PaO₂ and EVLW, and observed how the conventional continuously measured hemodynamic variables changed compared with ITBV and CI.

2. In septic shock patients norepinephrine might be harmful for the splanchnic circulation. Our aim was with the study to investigate whether ICG-PDR improves in septic shock patients when norepinephrine is combined with dobutamine in a one-hour long treatment.

3. The hepatocyte protective effect of NAC has not been examined during liver resection. The aim of our study was to investigate the effect of NAC prophylaxis on the postoperative conventional and dynamic liver function (ICG-PDR, LiMON) tests following liver resection.

4. CeVOX monitor was developed for continuous central venous saturation monitoring (Pulsion Medical Systems, Munich Germany). The aim of our study was to compare the accuracy of the CeVOX monitor measuring continuous central venous saturation (ScvO₂) with laboratory blood gas oxymetry under clinical circumstances.

4. Patients

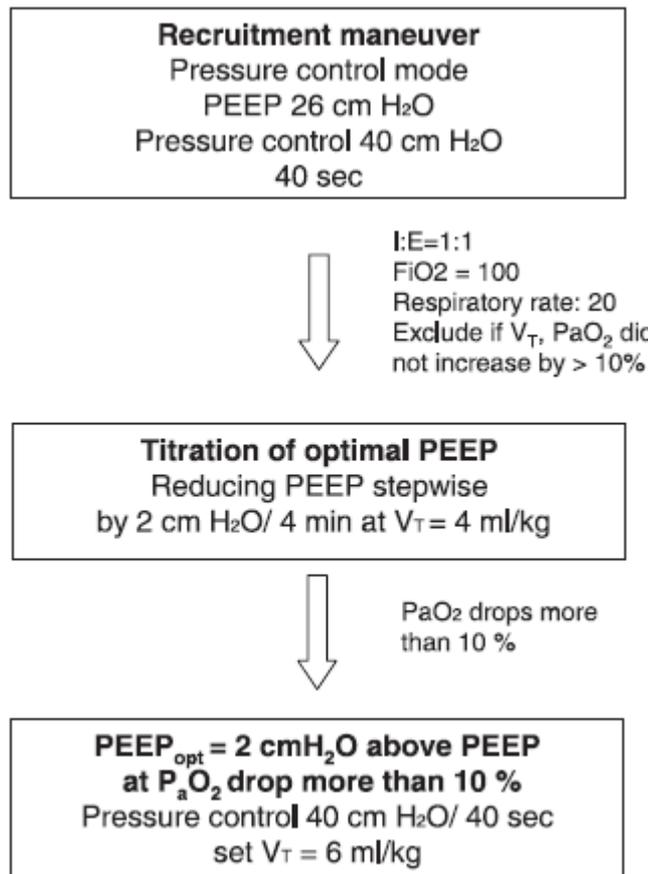
The Local Ethics Committee approved our studies, and informed consent was obtained from patients or their relatives. For our lung recruitment study every mechanically ventilated patient with an acute onset (<24 hrs) of ARDS (lung injury score $\geq 2,5$) was considered eligible for the study. Septic shock patients being stabilized by norepinephrine infusion were included in our norepinephrine – dobutamin treatment auto control, prospective study. The inclusion criteria were first measured ICG-PDR had to be < 18 %. Patients with chronic hepatic disease were excluded. Eligible for the CeVOX study were all critically ill patients requiring hemodynamic monitoring and central venous saturation could be measured by them. The study was performed in collaboration of the following centers: Technical University of Munich, Sheba Medical Centre, Tel-Aviv; Klinikum Oldenburg GmbH; Medical Center Cologne –Merheim; HELIS Klinikum Erfurt. Patients whose tumors were considered to be resectable were randomly assigned in our NAC – study, in a prospective, randomized, placebo controlled clinical trial following informed consent was obtained. Patients had undergone extended (more than one lobe) liver resection because of primary liver tumor, liver metastasis or haemangioma.

5. Methods

Lung recruitment

Hemodynamic parameters were measured by PiCCO monitor during the lung recruitment procedure. Patients were sedated and paralyzed during the procedure. Mechanical ventilation was performed in pressure control mode with FiO₂ 1,0, respiratory rate of 20, and inspiratory/expiratory ratio of 1:1. After 4 mins of stabilization basic measurements were repeated and recorded as baseline (T₀) values, and then lung recruitment and PEEP titration were started. Lung recruitment was performed as shown in Figure 1.

Figure 1.: Lung recruitment protocol



PEEP was set at 26 cm H₂O and then 40 cm H₂O of pressure amplitude was applied for 40 secs (40/40 maneuver). If there was no improvement in the tidal volume (V_T) or in the PaO₂, patients were considered to have nonrecruitable lungs with this recruitment maneuver and were withdrawn from the trial. After the opening procedure, the pressure control was reduced to reach a V_T of 4 mL/kg to exclude tidal recruitment; hence only the PEEP could be considered responsible for maintaining the alveoli open. Permissive hypercapnia was allowed to a pH of 7.15. Optimal PEEP was then determined in a way that PEEP was reduced stepwise from 26–2 cm H₂O in every 4 mins. At the end of every 4-min period, arterial blood samples were taken for blood gas analysis. The optimal PEEP was defined as 2 cm H₂O above the level of PEEP, where the PaO₂ dropped by 10%. After setting the PEEP at the optimal level, the 40/40 maneuver was applied again and the tidal volume was set as 6 mL/kg. To standardize circumstances, the FiO₂ was left at 100% until the end of the trial period of 1 hr in every patient.

Norepinephrine and dobutamine treatment

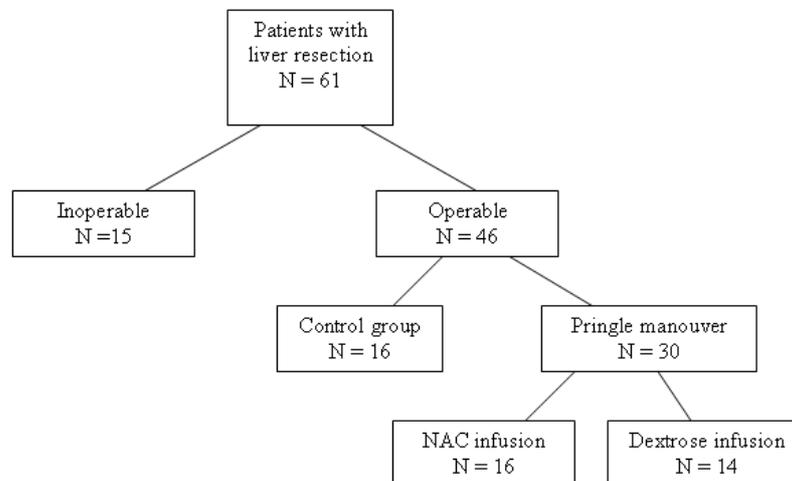
Patients with fluid unresponsive hypotonia were stabilized by norepinephrine and we started invasive hemodynamic monitoring by them. The endpoint of norepinephrine treatment was adequate preload (ITBV > 850 ml/m²), arterial mean pressure > 70 mmHg, CI > 3 L/m² and/or 65-70% ScVO₂. We started dobutamine therapy when measured ICG-PDR < 18 % (Dose of ICG: 0.25 mg/kg). Dobutamine infusion (0.5 µg/kg/min) lasted one hour long, as we measured again ICG-PDR and recorded the hemodynamic parameters. (T₁). Following hemodynamic parameters were recorded: HR, MAP, CVP, CI, SVI, ITBVI, EVLWI, dP/dt,

and laboratory parameters: blood count, blood gas, liver and renal function, PCT, CRP were recorded at T₀ és T₁ time point.

NAC protective effect during liver resection on ischemia-reperfusion

61 patients undergoing liver resection were randomized into three groups. Patients in the NAC group got 150 mg bolus NAC at the beginning of the operation followed by a continuous infusion 12 mg/kg/h during the surgery. Patients in the placebo group (P) received the same amount 5% dextrose infusion. In these two groups the intermittent Pringle maneuver was applied by the surgeon and consisted of cross-clamping the hepatoduodenal ligament about for 20 minutes and releasing the clamp for 5 minutes at the time of the resection. In the control group (K) the patients had undergone a routine liver resection without NAC and clamping.

Figure 2: Randomization of patients undergoing liver resection



Measuring ScvO₂ with CeVOX monitor

The CeVOX probe (PV2022-37; Pulsion Medical Systems, Munich, Germany) was inserted as described in the device's user's manual. The position of the probe in the superior vena cava was controlled by chest X-ray; thereafter, the system was calibrated in vivo to ScvO₂ measurements by laboratory co-oximeter. The standard volume of 1.5 ml blood was drawn from the same lumen through the catheter's Y-adapter every 8 h for ScvO₂.

6. Statistics

Statistical analysis were performed with SPSS for Windows (Statistical Program for Social Sciences, SPSS version 11.5). Significance level was given as $p < 0.05$ in each study. If data showed normal distribution data are shown as mean \pm SD. In cases of not normal distribution data are shown as median. Data are presented as box-plots in the figures. The statistical difference between the time points were analyzed by paired T-test. If the relationship between the data was important we performed Pearson's correlation test. In our lung recruitment study the number of the patient in the later time points was below 10, so we applied Wilcoxon test and not paired T-test. In our liver resection study we chose the PDR

value measured at 24 hour as the primary endpoint for our statistical analysis. To ensure 80% power for our study based on our previous PDR measurements and to show at least 5% difference between the groups if $p < 0.05$ we needed approximately 20 patients per every group. Because of financial causes we could not recruit enough patients to our study, so our data are preliminary. Based on retrospective ScvO₂ data a sample size calculation was performed. To reach 80% power with a $p \leq 0.05$ and the smallest difference not to be overlooked between CeVOX and blood gas analyser measured values of $\geq 5\%$, 750 pairs of data were needed from approximately 50 patients. The mean values measured by the CeVOX catheter and by blood gas machines were compared using Student's *t*-test. Correlation between the values was evaluated by calculation of Pearson's correlation. Agreement between the two measurements was tested by calculating the systemic error (bias), as described by Bland and Altman.

7. Results

The effect of lung recruitment on ventilation and hemodynamic parameters

Oxygenation improved significantly after the recruitment maneuver (T_{26R}) compared with the baseline (T₀) and remained significantly elevated for 30 mins (T₃₀). The baseline PEEP (17 ± 3 cm H₂O) and the optimal PEEP (15 ± 4 cm H₂O) did not differ significantly. On study entry, patients were hemodynamically stable. In two patients it was necessary to increase the inotropic support during the recruitment maneuver due to a decrease in CI below 2.5 L/min/m², but regarding the whole sample patients remained hemodynamically stable, and none of the patients needed additional fluid replacement. Heart rate remained almost unchanged during the investigation (Table 1.). Mean arterial pressure increased at T_{26R} but then remained significantly lower compared with T_{26R} but not with T₀. After the opening procedure, CI decreased significantly (T_{26R}) and then significantly and continuously increased as PEEP was being reduced until Tend (Fig. 3).

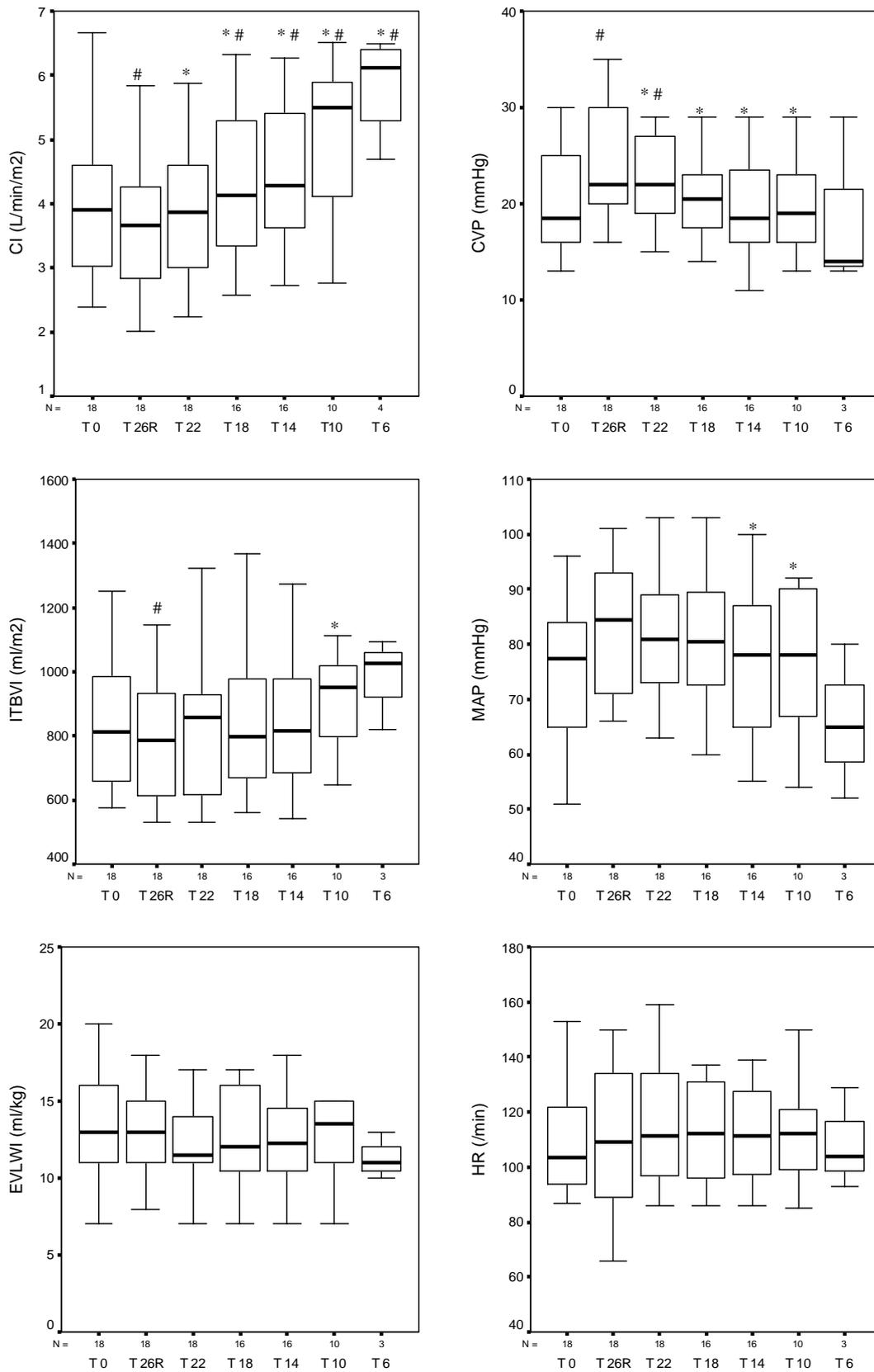
Table 1. Respiratory and hemodynamic changes at the five main stages

	T ₀	T _{26R}	T _{end}	T ₃₀	T ₆₀
pH	7.27 ± .07	7.22 ± .06 ^a	7.22 ± .06 ^a	7.27 ± .06 ^b	7.39 ± .06
Paco ₂ , mm Hg	49 ± 13	57 ± 14 ^a	56 ± 11 ^a	49 ± 11 ^b	47 ± 9.2
Pao ₂ , mm Hg	203 ± 108	328 ± 132 ^a	322 ± 101 ^a	266 ± 121 ^a	254 ± 118
PIP, cm H ₂ O	36 ± 5	43 ± 8 ^a	33 ± 7 ^{a,b}	34 ± 8 ^b	34 ± 9 ^b
PEEP, cm H ₂ O	17 ± 3	26 ± 0 ^a	15 ± 4 ^b	15 ± 4 ^b	15 ± 4 ^b
V _T , mL	523 ± 214	342 ± 63 ^a	479 ± 118 ^b	506 ± 110 ^b	502 ± 106 ^b
Heart rate, beats/min	109 ± 19	109 ± 25	113 ± 19	107 ± 18	106 ± 19
MAP, mm Hg	77 ± 13	83 ± 11	73 ± 11 ^b	76 ± 14 ^b	78 ± 12
CVP, mm Hg	20 ± 5	24 ± 6 ^a	19 ± 5 ^b	20 ± 6 ^b	20 ± 6 ^b
CI, L/min/m ²	3.90 ± 1.04	3.62 ± 0.91 ^a	4.21 ± 1.11 ^b	3.85 ± 1.12	3.88 ± 1.03
SVI, mL/m ²	37 ± 9	32 ± 8 ^a	36 ± 9 ^b	36 ± 10 ^b	36 ± 9
ITBVI, mL/m ²	832 ± 205	795 ± 188 ^a	814 ± 257	878 ± 245 ^b	852 ± 212
EVLWI, mL/kg	15 ± 8	15 ± 9	15 ± 8	14 ± 5	15 ± 7
NE, µg/min	13.0 ± 8.8	14.0 ± 8.7	14.6 ± 9.6	14.0 ± 9.7	14.4 ± 9.2
Dob, µg/kg/min	6.5 ± 4.7	8.0 ± 8.0	8.0 ± 8.0	9.0 ± 8.0	4.0 ± 2.0

T₀, baseline; T_{26R}, 4 mins after the recruitment maneuver at a positive end-expiratory pressure of 26 cm H₂O and tidal volume of 4 mL/kg; T_{end}, 40/40-manuever was repeated and tidal volume set at 6 mL/kg; T₃₀, 30 mins; T₆₀, 60 mins; PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; V_T, tidal volume; MAP, mean arterial pressure; CVP, central venous pressure; CI, cardiac index; SVI, stroke volume index; ITBVI, intrathoracic blood volume index; EVLWI, extravascular lung water index; NE, norepinephrine, Dob, dobutamine.

$p < .05$ compared with T₀; $p < .05$ compared with T_{26R}. Data are presented as mean ± SD.

Figure 3: Hemodynamic parameters' changes during lung recruitment



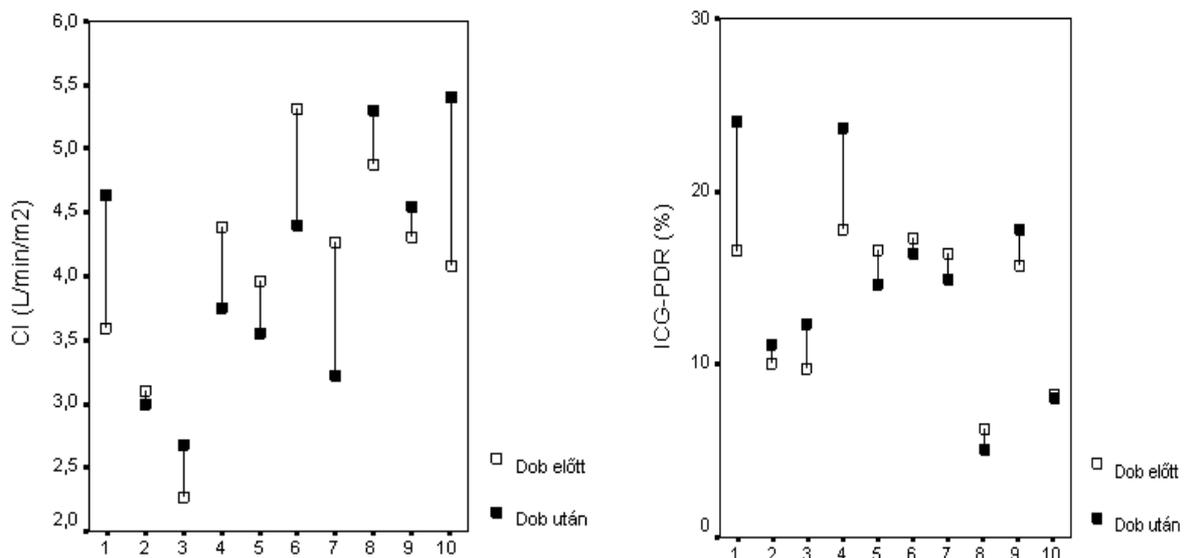
Data are presented as box-plot (minimum, maximum and mean). CI: cardiac index; CVP: central venous pressure; ITBVI: intrathoracic blood volume index; MAP: mean arterial pressure; EVLWI: extravascular lung water index; HR: heart rate. # $p < 0.05$ compared to T₀; * $p < 0.05$ compared to T_{26R}

Despite the finding that there was a significant positive correlation between CI and HR, as the latter did not change during PEEP titration, the observed change in CI was mainly due to changes in stroke volume rather than changes in HR as shown in Figure 2. There was a temporary “rebound” increase in CI at T_{end} compared with baseline, but then it returned to prerecruitment values by T_{30} and T_{60} . The preload indicators such as the central venous pressure and ITBVI changed inversely during the investigation. There was a moderate positive correlation between the CI and the ITBVI, a significant negative correlation between the CI and central venous pressure, and no significant correlation between CI and MAP.

Norepinephrine and dobutamine treatment in septic shock

By patients stabilized by norepinephrine less than 18 % ICG-PDR dobutamine was combined. We couldn't find significant difference in any of the hemodynamic parameters measured in the two time points (T_0 and T_1), and every parameter remained in the normal range. Administering dobutamine did increase neither cardiac index, nor heart rate. But if we look at the cases one by one (Figure 4-5) by 5 patients CI increased (3.8 ± 0.98 , 4.5 ± 1), by 5 it decreased (4.2 ± 0.8 , 3.6 ± 0.5), but on the whole - considering the low patient number - we could not find significant differences between the two groups. Illustrating the changes in CI and ICG-PDR data measured at T_0 and T_1 in each case it is visible, that increase or decrease changes in CI were not followed by the similar changes in PDR. On the whole ICG-PDR increased slightly along the one hour treatment, but there was no significant difference between the 2 time points (T_0 : 13.4 ± 4.3 vs. T_1 : 14.78 ± 6 %, $p= 0.22$).

Figure 4-5: CI and ICG-PDR changes in cases at T_0 and T_1

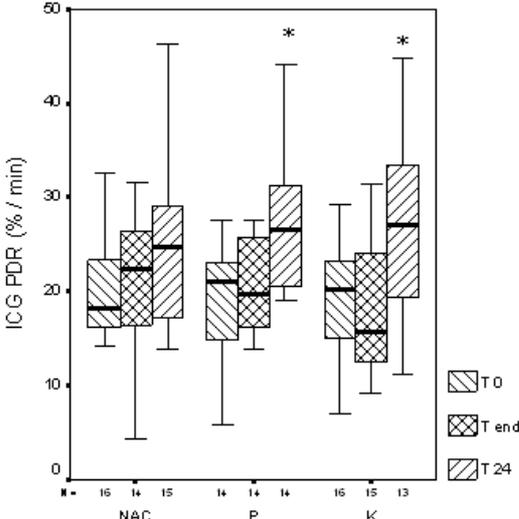


NAC effect on liver resection

61 patients were randomized into the 3 groups, but 14 patients had to be excluded because of inoperability and 1 patient died during the operation because bleeding could not be ceased. For the final analysis we could use 46 patients' data, which had undergone a successful liver resection. Distribution of etiologic causes of the liver resection is the following: liver metastasis: 45, primary liver tumor: 11 and haemangioma: 4 cases. Considering age, gender, operation time and the clamping time there was no significant difference between the groups,

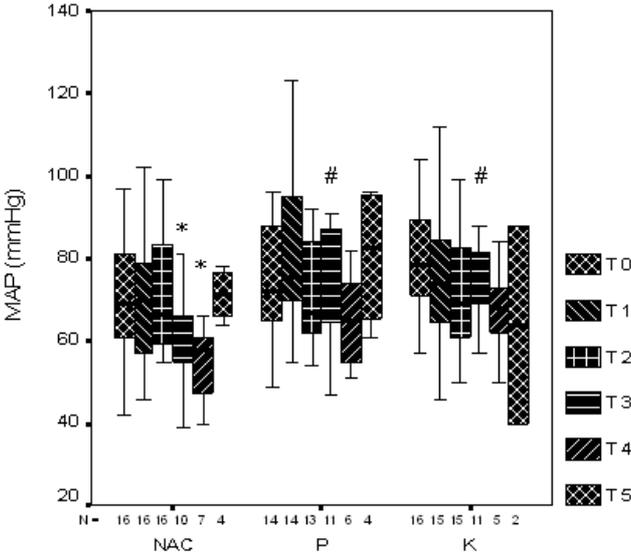
the randomization was successful (Table 1). The operations were performed by the same surgeon and he decided in the question of operability. There were no postoperative complications in any of the patients, such as ascites, liver failure, encephalopathy, jaundice, hypoalbuminemia, hyperbilirubinemia, bleeding. All of our patients were discharged back to the Surgical Department from the Intensive Care Unit without any complications.

Figure 6: ICG PDR and ICG R-15 in the three groups at the beginning (T₀), At the end (T_{end}) and 24 hours after the surgery (T₂₄)



Data are presented as median, minimum, maximum and interkvartile ranges
 ICG PDR: indocyanine green disappearance rate
 ICG R-15: indocyanine green retention rate at 15 min
 *, p<0.05 vs. T₀

Figure 7: Intraoperative hemodynamic changes



MAP – mean arterial pressure, T₀ – baseline measurements, T₁-2...: measurements every hour.
 Data are presented as median, minimum, maximum and interkvartile ranges.
 *, p < 0.05 vs T₀, # : p < 0.05 between groups

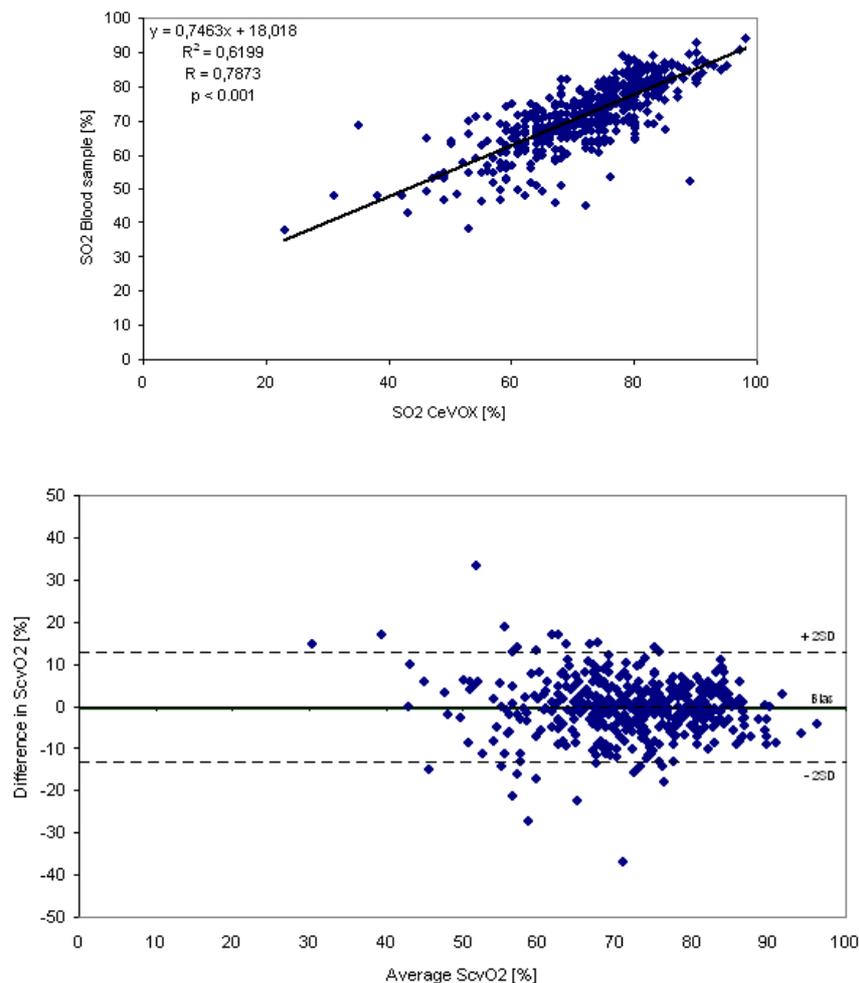
In the NAC group the mean arterial pressure decreased significantly in the 4th hour of the surgery, and remained significantly lower in the 5th hour compared to the P and K groups and

the baseline measurement (Figure 1). In other hemodynamic parameters such as heart rate, CVP and central venous saturation (ScVO₂), there were no differences between the groups (data not shown). The CVP and ScVO₂ did not change significantly according to the baseline measurements in each time points.

We did not monitor directly the blood loss during the operation, but recorded every hour the value of the hemoglobin based on the arterial blood gas analysis. There were no differences between the groups, or in the number of patients who required blood transfusion. We recorded the intraoperatively substituted fluid amount, which was almost the same in the three groups (Table 2, Table 3).

CeVOX and co-oximetry measurement

There was no significant difference between the ScvO₂ values measured by the CeVOX catheter and the laboratory results (mean 72.2± 9.9 vs 71.9± 9.6%, respectively, $p = 0.44$; 95% confidence interval, CI: lower = -0.3, upper = 0.8). The mean difference between the ScvO₂ values (blood gas analyser — CeVOX) was -0.3 [-6.4, 5.7] %. There was significant correlation between ScvO₂ as measured by the CeVOX and the results determined by conventional blood gas devices (Fig. 1). Bland and Altman plotting showed that the mean difference between the means (bias) was -0.3, with lower and upper levels of agreement of -13.2 and 12.5 (Fig. 1).



Relationship between ScvO₂ measured in vitro (co-oximetry) and in vivo (CeVOX) in the whole sample. The upper panel gives the linear regression analysis (dotted lines indicate the 95% confidence interval). The lower panel gives the difference between methods according to Bland and Altman

The percentage error (limits of agreement divided by the mean ScvO₂) was 35.5% (95% CI 35–36%). When using only the first time point ($n = 53$) we found a comparable correlation ($r = 0.79$, $p < 0.001$) and agreement (mean bias -0.6% , limits of agreement -13.6 and 12.4) (Fig. 2 in the electronic supplementary material, ESM). Furthermore, for the between-subject correlation a weighted correlation coefficient of $r = 0.96$ ($p < 0.001$) was found. With respect to the within-subject correlation, there was also a significant but less pronounced correlation ($r = 0.56$, $p < 0.001$). When comparing the changes in both techniques ($n = 50$ patients with more than one simultaneous measurement) we found $r = 0.58$ ($p < 0.0001$).

8. Discussion

Lung recruitment in patients with ARDS

PaO₂ and EVLW

This study showed that the applied technique of lung recruitment was effective in improving the PaO₂ significantly, which was not followed by a reduction in the EVLW. The other main finding of this study is that CI alters significantly as intrathoracic pressures vary, but neither the CVP nor the MAP or the HR can reflect these changes.

In a recent review of ARDS, four mechanisms have been proposed to explain improved pulmonary function and gas exchange with PEEP: 1) increased functional residual capacity, 2) alveolar recruitment, 3) redistribution of extravascular lung water, and 4) improved ventilation-perfusion matching. The relationship between EVLW and oxygenation is controversial. In early clinical studies correlation between oxygenation and EVLW was found to be poor. In a recent animal experiment, increasing the PEEP from 10 to 15 cmH₂O was followed by an increase in oxygenation without any decrease in the EVLW. Results of our current study are in accord with this latter finding. The message of the current trial is that by increasing PEEP and inflation pressure although significantly increase the PaO₂, but it is not followed by rapid changes in EVLW. Whether there is any relationship between the EVLW and the optimal PEEP, cannot be answered at present due to the small sample size (only 18 data points), hence the continuation of the study is required.

Although, there was a significant improvement in PaO₂ after the recruitment and at T_{end}, the baseline and the optimal-PEEP did not differ significantly. In fact, the optimal-PEEP was fraction lower than at the start. This could be explained by our ventilation protocol, in which we use relatively high PEEP levels as compared to the protocol used in the ARDS Network trial. The finding that PaO₂ dropped at T₆₀ may be due to absorption atelectasis caused by the study protocol in which after T_{end} the same ventilator settings with an FiO₂ of 1.0 were applied throughout the observation of 60 minutes.

Hemodynamic parameters

Increased intrathoracic pressures may compromise cardiac function via several mechanisms. High pressures can impair venous return hence decrease preload, or can exert a direct compression on the cardiac fossa and the caval veins. The compression on the right atrium and the pulmonary vessels is significant and impede the filling of the heart and the outflow from the right ventricle. In a recent animal experiment it was found, that increasing levels of PEEP up to 14 cmH₂O did not compromise left ventricular end diastolic volume and ejection fraction, but at PEEP of 21 cmH₂O left ventricular preload and the stroke volume decreased significantly. In another clinical trial there was significant decrease in CI when PEEP was increased from 10 to 15 cmH₂O. In our study we found similar results, although the PEEP levels (ranging from 15 ± 4 to 26 cmH₂O) were considerably higher, throughout the

measurements. Nevertheless, decreasing the PEEP from 26 cmH₂O was followed by a continuous increase in CI.

Due to the decrease in CI one might expect a drop in MAP associated with tachycardia. On the contrary we found that MAP increased till T_{26R} during the opening procedure and then decreased significantly by T_{end}. There was no significant change in the HR throughout the investigation. Lim et al., reported increased blood pressure as well as heart rate that returned to pre-recruitment manoeuvre levels in 15 minutes, perhaps reflecting sympathetic response to the prolonged recruitment manoeuvre they used. Medoff et al. and Villagra et al. reported that blood pressure and heart rate remained stable during the recruitment manoeuvre. These results are in accord with our findings, that monitoring of changes in arterial pressure and HR do not reflect the true effects of recruitment manoeuvre on cardiac output.

It was found, that in mechanically ventilated patients especially at high intrathoracic pressures ITBV is superior to cardiac filling. The results of our study provide further support of this statement. However, the disadvantage of ITBV is that it cannot be measured continuously. As the continuation of this trial, in a pilot study of 10 patients we found that ScvO₂ showed a significant positive correlation with CI (r=0.432, p=0.002). This preliminary data suggests that continuous ScvO₂ monitoring may be an alternative to invasive CO measurements during lung recruitment in emergency situations.

Norepinephrine and dobutamine therapy

Because of the small patient number our study is only preliminary. Based on our results dobutamine added to the norepinephrine treatment did not cause significant changes in the hemodynamic parameters and the indocyanine green excretion during the 1 hour long infusion. Only half of the patient answered on the treatment, however this was not followed by any ICG changes.

One objection against norepinephrine is that its vasoconstrictive effect might worsen the hepato-splanchnic circulation. Martin et al with 197 patients proved that administration of norepinephrine improved patients' outcome. They concluded that norepinephrine didn't caused hypoperfusion in the organs, and did not lead to multiorgan failure. The combination of norepinephrine and dobutamine is examined most of the time, because its combination enables us to use both of their vascular and cardiac effect changing their ratio.

Studies, which examined dobutamine cardiac effect in septic shock patients observed an increase in the CI, caused by the increase in heart rate and stroke volume. In our preliminary study dobutamine did not change heart rate or cardiac index. In a similar French study with 330 patients they could not find any differences by patients treated with norepinephrine plus dobutamine or epinephrine. There were no differences in the hemodynamic parameters or the surviving rate. Patients' cardiac index was in the normal range at the T₀ time point. Dobutamine combined with norepinephrine increased CI by 5 patients, till by 5 patients it decreased. It is supported by some other findings, when septic shock patients showed an increase in CI and DO₂I on dobutamine treatment, and this could be a prognostic factor also. Jellema et al. administered dobutamine in a rising dose. Patients with a positive chronotropic response to dobutamine had lower baseline HR values, and a chronotropic rather than inotropic response predicted an increase in cardiac index and systemic oxygen delivery index. Our study should be continued to establish whether patients can be non-respondent to dobutamine treatment.

We couldn't prove the improvement of ICG-PDR by patients treated with norepinephrine and dobutamine. ICG-PDR helps to draw a picture about the functional state of the liver and shows the functional impairment on cellular level as well. Based on Joly et al. work dobutamine did not have significant effect on hepatocyte ICG excretion despite in their study the systemic hemodynamic parameters improved. ICG excretion is used to examine liver perfusion, because it is perfusion dependent. They did not find significant difference in the ICG excretion after a one hour long dobutamine (dose: 7.5 $\mu\text{g}/\text{kg}/\text{min}$) infusion. They explained their results: dobutamine does not increase the blood supply of the liver, or if it is increased, hepatocytes are unable to take up ICG because of their altered metabolism.

NAC prophylaxis in liver resection

Liver is an organ with rich vasculature. Intraoperative blood loss can be a risk factor for postoperative morbidity. Common feature of the surgical methods is the vascular control, when the circulation of the liver is excluded somehow from the systemic circulation. This way we are able to control the bleeding, but we might cause hemodynamic intolerance. The surgeon applied Pringle maneuver in our study. In our study we also could not find significant differences between the control and the placebo group in the hemodynamic parameters recorded every hour during the operation time. Man et al. described the advantages of this method in a prospective randomized study such as: less intraoperative blood loss and less alteration in postoperative liver function. Using the maneuver shortened the time to complete the resection too. In our study there was no difference in the operation time between the three groups. Although we did not measure the blood loss directly, none of the three groups' patients required more blood transfusion during the surgery, and even the hemoglobin levels were similar in the one-hour periods during the liver resection.

Disadvantage of vascular occlusion might be the warm ischemia reperfusion in the liver, which leads to cellular injury. This process contributes to the development of oxygen free radicals and it will result in oxidative stress. Free radicals can be eliminated by giving exogenous antioxidants, such as N-acetylcysteine. In septic patients NAC reduced Bi level, what we could not observe in our study. The difference can be that septic shock is a long lasting toxicity for the liver, till liver resection causes ischemia only for 30-40 min. Beside the antioxidant profile another explanation for the improvement in liver function might arise from the hemodynamic effects of NAC. Many studies described that NAC improved the systemic and regional hemodynamic and oxygen transport in acute liver failure of various origin. Devlin et al. for example described increased oxygen consumption and ICG clearance by ventilated patients with liver failure. We found that in the placebo and control group the ICG clearance decreased at the T_{end} while in the NAC group it showed a moderate improvement, what did not prove to be significant. We recorded also a significant decrease in the in the MAP for the 4th hour of the surgery in the NAC treated group, what could be observed in the 5th hour also. However this was not followed by a decrease in the central venous oxygenation, or an increase in the heart rate. Other groups remained stable hemodynamically during the operation time.

For assessing liver function in the perioperative period we have two possibilities: routine laboratory tests, the so called static tests and dynamic liver function tests. Conventionally measured laboratory tests, such as the bilirubin, the serum liver enzymes (ALT, AST), and the proteins (PTT, albumin) synthesized in the liver are not able to track the changes in the liver function quickly enough, only with latency. The dynamic assessment of the liver function means a function performed only by the liver, such as clearance of substances (e.g. indocyanine green, ICG). ICG-PDR proved to be superior to bilirubin in terms of outcome prediction and indicated earlier the liver dysfunction. During our study we

measured both the conventional (Bi, PTT, Albumin, AST, ALT) and dynamic tests (ICG-PDR) for the assessment of liver function. Currently there is no exact definition for liver failure regarding laboratory parameters, so it is hard to define what the early laboratory warning signs are. General studies examine the kinetics of liver enzymes, prothrombin and bilirubin postoperatively. Balzan et al. described the kinetics of the laboratory measurements in their study. The prothrombin level reaches its minimum on the first postoperative day and increases to the preoperative level on the 5th day. The bilirubin increases until the 3rd day and thereafter slowly decreases to day 7. In another study the liver enzymes reached a peak on postoperative day 1 or 2 and returned to normal by days 7 to 10. Balzan defined the indicator of postoperative liver failure as the 50-50 criteria, meaning a PT < 50% or SeBi > 50 µmol/L (3 mg/dl) on the 5th postoperative day. By none of our patients enrolled in the study developed liver failure during their hospital stay. The AST, ALT showed significant and pathological increase following the surgery, however the most likely reason for it is the tissue injury caused by the resection. The level of prothrombin and albumin decreased, but we did not get bleeding and there was no edema formation. Bilirubin increased slightly but remained in the normal range. The PDR increased to the T₂₄ in all of the three groups, but it was significant only in the placebo and control group. This is contrary to the findings that the reduced liver volume decreases the PDR. The explanation for our findings might be based on a study by Thasler and colleagues. They examined the hemodynamic changes following major liver resection. In the hepatectomy group, the ICG clearance decreased rapidly during the intraoperative phase of liver resection but returned to the preoperative values at the end of surgery. After liver resection a rapid normalization of liver function (ICG clearance) was observed, indicating an increase in blood flow to the remnant parenchyma and they could observe a hyperdynamic circulation with increased CI and unchanged MAP.

Based on our preliminary results it seems that only the Bi and PDR can be relied on for monitoring the real physiological changes in liver function after liver resection. This is in accordance with the results of a recent study.

Continuous central venous saturation measurement

In the current multicentre clinical study we compared in vivo fiberoptic ScvO₂ measurements with the CeVOX monitor to ScvO₂ determined by laboratory co-oximetry. It was found that values measured by the CeVOX fiberoptic catheter showed good correlation with laboratory values. The Bland and Altman plots showed moderate agreement with laboratory-measured ScvO₂. In certain situations tissue hypoxia may exist despite normal global hemodynamic figures. There is increasing evidence that measuring ScvO₂ is a simple alternative to SvO₂ as an indirect index of tissue oxygenation. According to recent studies ScvO₂ allows early detection of hemodynamic instability. Compared with increased lactate or metabolic acidosis, ScvO₂ may indicate inadequate oxygen delivery earlier. For the measurement of ScvO₂ co-oximetry is the standard procedure. However, continuous monitoring of ScvO₂ may be indicated in patients with acute illness who are at risk of developing sudden hemodynamic instability and low cardiac output. Once this is confirmed, invasive hemodynamic monitoring of cardiac output and preload is recommended. There are two technologies currently available utilizing a fiberoptic probe for continuous measurement of ScvO₂: the PreSep (Edwards Lifesciences, Irvine, USA) and the CeVOX monitor. The advantage of the latter is that it can be inserted into any central line already in place. Our results regarding the accuracy of CeVOX under clinical circumstances are comparable to result reported previously. In the current investigation ScvO₂ measured by CeVOX showed good correlation.

9. Novel findings

- 9.1. Following lung recruitment and descending optimal PEEP titration, the PaO₂ improves significantly, without any change in the EVLW up to 1 hour. This suggests a decrease in atelectasis as a result of recruitment rather than a reduction of EVLW. There is a significant change in CI during the maneuver, but neither central venous pressure, heart rate nor MAP can reflect these changes.
- 9.2. For amelioration of the ischemic/reperfusion injury following liver resection the NAC prophylaxis did not prove to be effective based on our recent study. Our results showed that the intraoperative administered NAC prophylaxis caused hemodynamic instability in patients, until it did not influence the postoperative liver function significantly, therefore the routine application of NAC in liver resection is not supported by our results. Out of the routine laboratory tests only Bi and the dynamic test ICG PDR proved to be useful for monitoring liver function.
- 9.3. There was no significant difference between ICG – PDR after dobutamine infusion. When dobutamine increased CI it was not followed necessarily by an increase in ICG-PDR. Based on our results dobutamine has no obvious effect on ICG-PDR.
- 9.4. The results in a heterogeneous group of critically ill patients show that continuous ScvO₂ monitoring by the CeVOX technology gave comparable results to that measured by laboratory co-oxymetry and therefore, can be relied on in the everyday clinical practice, particularly when monitoring the trend of ScvO₂ is desired.

10. Acknowledgements

I would like to express my deepest gratitude to Professor Zsolt Molnár for letting me commence my work as his Ph.D. student. He introduced me as a medical student to scientific research and ensured his invaluable assistance, kind support and graceful guidance over the years for my development. He also showed me how we should respect our patients whilst being human to them. I would like to thank to Tamás Szakmány MD, PhD, for his unselfish support, that he – as my ancestor - helped me to start my research work. I would like to thank to Tamás Leiner MD, to András Mikor MD and Krisztián Tánczos MD, who were always there when I needed help, and who let me to share my dilemmas. I would like to thank to Professor Lajos Bogár for his help that I could work in the Institute of Anesthesiology and Intensive Therapy. I express my thank to Tamás Kőszegi MD and Ibolya Orosz for their help in the laboratory measurements at the beginning. I would like to acknowledge all the doctors at the Institute for their support and help to me, as the beginner colleague, that they taught me and helped me with their advices. I would like to thank all the nurses (especially to Judit Gubányi) and anesthesiology assistants at the Institute for their extra work helping us to perform our studies beside their basic work. I gratefully acknowledge everyone who has taken part of this project for their constant support, which has made it possible to complete this dissertation.

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