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# Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium☆

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**Abstract**

**Objective:** Patients undergoing cardiac surgery procedures are thought to be at risk of early neuropsychological deficits and delirium. Regional cerebral hypoperfusion may play a role in the etiology of this complication. We hypothesized that low systemic perfusion pressure during cardiopulmonary bypass (CPB) would correlate with early postoperative cognitive dysfunction in on-pump patients. **Methods:** In this prospective, randomized, single-center trial, we assigned 92 patients scheduled for elective or urgent coronary artery bypass grafting (CABG) to high-pressure (HP: 80—90 mmHg, $n = 44$) or low-pressure (LP: 60—70 mmHg, $n = 48$) perfusion groups during CPB. Patients with prior cerebrovascular or psychiatric disorders were excluded. Primary end point was the cognitive outcome as measured by Mini-Mental-Status examination before and 48 h after surgery. **Results:** Patients' pre- and intra-operative characteristics did not differ between groups. Significantly more patients in the LP group developed postoperative delirium than in the HP group (LP 13%. vs HP 0%, $p = 0.017$). The postoperative drop in Mini-Mental-Status scores was significantly greater in the LP group (LP $3.9 \pm 6.5$ vs HP $1.1 \pm 1.9$; $p = 0.012$). No group differences were detected in cerebral oxygenation measured by near-infrared spectroscopy during CPB. The LP group's postoperative arterial lactate concentration in the intensive care unit was significantly higher as compared with the HP group (LP $2.0 \pm 1.1$ mmol $l^{-1}$ vs HP $1.4 \pm 0.6$ mmol $l^{-1}$; $p < 0.001$). We observed no differences between the groups in any other postoperative clinical, functional, or laboratory parameters. **Conclusion:** Maintaining perfusion pressure at physiologic levels during normothermic CPB (80—90 mmHg) is associated with less early postoperative cognitive dysfunction and delirium. This perfusion strategy neither increases morbidity, nor does it impair organ function.


*Keywords:* Coronary artery bypass grafting; Cardiopulmonary bypass; Perfusion pressure; Postoperative cognitive dysfunction

## 1. Introduction

Transient cognitive dysfunction following heart surgery is a cumbersome complication. The most severe presentation of transient cognitive dysfunction, postoperative delirium, occurs at a frequency of 3—32% [1,2]. Known risk factors for the development of delirium are previous neurological disorders, age, cardiopulmonary bypass (CPB) duration, periods of low cardiac output, peripheral vascular disease, a total European System for Cardiac Operative Risk Evaluation (EuroSCORE) over 5, preoperative intra-aortic balloon pump (IABP) support, and postoperative blood product usage. Regional hypoperfusion and the generation of microemboli during CPB are frequently reported reasons for postoperative cognitive dysfunction [3,4].

Perfusion pressure during CPB is often kept at levels that are lower than the physiologic mean arterial pressure (MAP). This is believed to be satisfactory, even though maintaining only a sufficient pump flow (resembling normal cardiac output before CPB) without any further intervention results in mean perfusion pressures below 60 mmHg in most patients. Nevertheless, there are studies supporting this strategy. Slogoff et al. [5] reported that 'failure of the native circulation during periods other than cardiopulmonary bypass rather than the flows and pressures (...) are the major cause of renal and clinically apparent central nervous system dysfunction after cardiac operations.' However, non-pulsatile perfusion is suspected to produce regional hypoperfusion, and may be one reason for elevated morbidity and mortality [6,7]. This regional hypoperfusion may be more pronounced with subnormal perfusion pressure.

We hypothesized that keeping perfusion pressure during CPB within physiological ranges would protect against early cognitive dysfunction after coronary bypass surgery.

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## 2. Materials and methods

### 2.1. Patient population

In this prospective, randomized, single-center trial, we examined patients scheduled for elective or urgent coronary artery bypass graft (CABG) surgery. Enrolment took place between January 2008 and February 2010. All patients underwent surgery at the University Medical Center Freiburg. Inclusion criteria were on-pump elective or urgent CABG. Patients with a history of cerebrovascular diseases (e.g., patients with carotid stenosis) or previous psychiatric disorders were excluded from screening. Other exclusion criteria were emergency surgery, preoperative instability (defined as patients who need to be at intensive care unit (ICU) preoperatively), concomitant surgery (valve, Maze, etc.), patients incapable of taking the neuropsychological test (i.e., language barriers), and those who could not give informed written consent. Patients were also excluded if the desired pressure during CPB was not achieved or post-operative cognitive evaluation was impossible. All patients gave written informed consent to participate in the study, safety was reviewed by our ethics committee, and the study was randomized by the ZKS (Center for Clinical Studies) Freiburg. Each patient was assigned to one of two groups differing only in perfusion pressure during CPB: the high-pressure group (HP group) with a target perfusion pressure of 80–90 mmHg, or the low-pressure group (LP group), whose target perfusion pressure was 60–70 mmHg.

### 2.2. Anesthesia, CPB, and perfusion pressure management

Anesthesia was initiated using 20 $\mu g\ kg^{-1}$ flunitrazepam, 5 $\mu g\ kg^{-1}$ fentanyl, and 0.1 $mg\ kg^{-1}$ pancuronium. For maintenance, we applied 1% minimum alveolar concentration of sevofluran, 10 $\mu g^{-1}\ kg^{-1}\ h^{-1}$ fentanyl, and pancuronium as required. The routine monitoring consists of central venous and arterial line plus Swan–Ganz catheter. Arterial blood pressure was monitored by an arterial line in the radial or brachial artery. Preoperatively, side differences were ruled out by non-invasive blood pressure management. As a simplification, perfusion pressure during CPB, in this study, is defined as the MAP. Whenever the central venous pressure, which was monitored invasively and continuously, was elevated during tilting of the heart, the MAP was elevated to maintain the actual perfusion for the organs. CPB was conducted non-pulsatile with HLM S3 (Sorin, München, Germany). We maintained a pump flow of 2.6 $l\ min^{-1}\ m^{-2}$ during normothermia (deepest body core temperature $> 35.5\ ^{\circ}C$) in all patients. We used an intermittent infusion of cold-blood cardioplegic solution for myocardial protection. Hematocrit was guided higher by 20% and pH was managed according the alpha-stat principle. Blood gas was measured at 20-min intervals. We treated arterial hypotension with norepinephrine (maximal dose 0.4 $\mu g\ kg^{-1}\ min^{-1}$) and hypertension with single 5-mg boli of urapidil (maximal dose 0.1 $mg\ kg^{-1}\ min^{-1}$). Perfusion pressure was recorded every minute and mean values were calculated. We considered the patient as having received adequate treatment whenever the mean value fell inside the range of 78–92 mmHg in the HP group and 58–72 mmHg in the LP group. Patients were also excluded when the standard deviation of the recorded MAP was excessive, due to perfusion pressure instability during pump run.

The occurrence of microemboli before and after a Dynamic Bubble Trap (DBT, Kardialgut, Munich, Germany) was measured, and the reduction rate documented. During CPB, cerebral oxygen saturation was measured with near-infrared spectroscope INVOS (Somanetics, Troy, USA) on both sides of the forehead.

For postoperative analgesia, we routinely applied metamizol, paracetamol, and piritramid as required. Whenever a delirium occurred, we counteracted with haloperidol or melperon on an individual selection basis.

### 2.3. Primary end point: neuropsychological examination

The primary end point of this study was cognitive outcome as measured by the Mini-Mental-State examination (MMSE) before and 48 h after surgery. The test was conducted by two trained persons blinded for the allocation into a group, and as generally reported and validated for cardiac surgery [8,9]. Any score 10 points under the preoperative score, together with a positive assessment by a psychologist, was considered delirium.

### 2.4. Secondary clinical end points

Complications, use of blood products, urinary output, maximum weight gain, ventilation time, and ICU- and total postoperative stay were documented according to the patients' records. Hemodynamics were assessed using a Swan–Ganz catheter directly after arrival to the ICU, as well as 4 and 24 h postoperatively. The parameters reported are cardiac index, MAP, central venous pressure (CVP), systemic vascular resistance (SVR), pulmonary capillary wedge pressure (PCWP), and pulmonary vascular resistance (PCWP). SVR was calculated as (MAP − CVP)/cardiac output and PVR was calculated as (mean pulmonary pressure − PCWP)/cardiac output. Arterial blood-gas analysis was carried out at the same time points (ABL800 FLEX, Radiometer, Willich, Germany). Creatinine concentration, hemoglobin concentration, C-reactive protein (CRP), and creatine kinase MB (CK-MB) were measured on the first, second, and seventh postoperative days, and whenever clinically indicated at the central laboratory of the University Medical Center Freiburg. Severe renal insufficiency was defined by requirement of dialysis or a creatinine concentration $> 3.0\ mg\ dl^{-1}$.

### 2.5. Statistical analysis

The study was designed to detect a minimal difference between groups of five, assuming a standard deviation of 10 with a two-sided significance level of 5% and a power of 80% using an independent two-sample *t*-test. Data were analyzed using a computerized statistical program (SigmaStat©, SPSS Inc., Chicago, IL, USA). Values are given as mean ± standard deviation. For normal distributed value, we evaluated differences between the groups with the unpaired student *t*-test. To compare pre- and postoperative scores, we used the paired *t*-test. Categorical values were compared

between the groups using Fisher's exact test or chi-square test. A $p$ value $<0.05$ was considered statistically significant.

## 3. Results

Of the 133 patients screened, 28 (21%) had a history of cerebrovascular disease and had to be excluded. The remaining patients were randomized. Patients whose targeted perfusion pressure was not maintained during the CPB run were excluded (five patients in the HP group). We decided after randomization that additional procedures (e.g., aortic valve replacement) were necessary in three patients, who were then excluded. A further four patients in the LP group LP and one in the HP group were excluded because the postoperative MMSE was not feasible while the patient was being ventilated and sedated. Our study cohort thus consists of 92 patients ($n$ = 48 in the LP and $n$ = 44 in the HP group).

### 3.1. Pre- and intra-operative characteristics

The preoperative characteristics reflect a typical cohort of CABG patients whereby the two randomized groups did not differ (Table 1).

The two groups' perfusion pressure differed highly significantly due to the nature of the study (MAP in group LP: $64.7 \pm 8.2$ mmHg and in group HP: $84.3 \pm 11.2$ mmHg, $p < 0.001$). The LP group's operative times were slightly longer without reaching statistical significance (Table 1).

### 3.2. Neuropsychological examination

We observed a statistically highly significant postoperative decline in MMSE scores in both groups (Fig. 1(a)). The LP group's pre- to postoperative decline was $3.9 \pm 6.1$ points, while the HP group's decline was $1.1 \pm 1.9$ points (comparison of differences $p = 0.012$). No one in the HP group experienced a delirium, whereas six patients (13%, $p = 0.017$) in the LP group presented a drop in MMSE of more than 10 points and a diagnosed delirium (Fig. 1(b)).

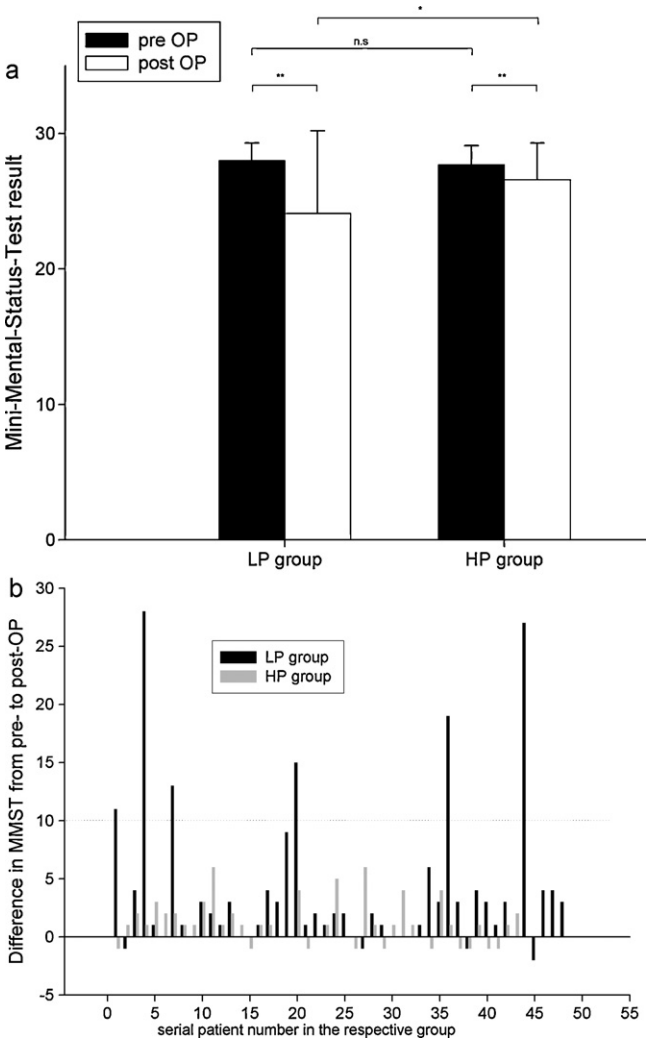


Fig. 1. (a) Results of the Mini-Mental-State examination in the group receiving high perfusion pressure during CPB (80–90 mmHg) and the group with low perfusion pressure (60–70 mmHg). The examination was given by a blinded person 24 h before and 48 h after surgery (*$p < 0.05$, **$p < 0.001$, n.s. = not significant). (b) Each patient's pre- and postoperative differences in Mini-Mental-State scores. Note that the scores of six patients (13%) in the LP group (black bars) dropped more than 10 points in the neuropsychological study; they were diagnosed as having a delirium.

Table 1. Preoperative and intraoperative characteristics.

| Variables | LP group (48 patients) | HP group (44 patients) | $p$-value |
|---|---|---|---|
| Age [years] | $65.2 \pm 9.6$ | $68.7 \pm 8.3$ | 0.06 |
| Male sex | 40 (83%) | 34 (77%) | 0.60 |
| BMI | $27.9 \pm 4.0$ | $28.0 \pm 4.2$ | 0.90 |
| Diabetes mellitus | 12 (25%) | 10 (22%) | 0.81 |
| Hypertension | 30 (63%) | 32 (72%) | 0.37 |
| Hyperlipidemia | 25 (52%) | 23 (52%) | 1.00 |
| Smoker | 23 (48%) | 13 (30%) | 0.09 |
| Alcoholic | 0 (0%) | 1 (2.3%) | 0.48 |
| Severe renal insufficiency | 5 (10%) | 7 (16%) | 0.54 |
| COPD | 3 (6%) | 4 (9%) | 0.71 |
| Preoperative arrhythmia | 5 (10%) | 6 (14%) | 0.75 |
| Logistic EuroSCORE [%] | $5.2 \pm 0.7$ | $5.4 \pm 0.6$ | 0.80 |
| Operative time [min] | $259 \pm 53$ | $247 \pm 52$ | 0.25 |
| CPB time [min] | $101 \pm 25$ | $91 \pm 30$ | 0.11 |
| ACC time [min] | $76 \pm 19$ | $71 \pm 23$ | 0.27 |
| No. of bypasses | $2.9 \pm 0.7$ | $2.7 \pm 0.7$ | 0.21 |

LP group: perfusion pressure 50–60 mmHg, HP group: perfusion pressure 80–90 mmHg, BMI: body mass index, COPD: chronic obstructive pulmonary disease, CPB: cardiopulmonary bypass, ACC: aortic cross clamp.

Table 2. Transcutaneous cerebral oxygen saturation as measured by near-infrared spectroscopy (NIRS) and reduction rate of microbubbles generated by the bubble trap.

| Variables | LP group (48 patients) | HP group (44 patients) | *p*-value |
|---|---|---|---|
| NIRS left | 68.4 ± 5.8 | 67.8 ± 5.9 | 0.73 |
| NIRS right | 68.3 ± 6.0 | 67.4 ± 6.0 | 0.63 |
| Reduced microbubbles [%] | 65 ± 13 | 65 ± 17 | 0.99 |

### 3.3. Secondary clinical end points

The transcranial cerebral oxygen saturation and micro-emboli reduction by the bubble trap did not differ between the groups (Table 2), nor did the absolute number of detected bubbles differ (data not shown).

Postoperative complications did not, for the most part, differ between the groups (Table 3). The frequency of atrial fibrillation was higher in group HP (36% vs 19%) without reaching statistical significance ($p = 0.065$). The HP group's ICU stay, ventilation time, and time until cessation of catecholamines tend to be shorter without reaching statistical significance. Postoperative hemodynamics were completely unaffected by the intervention, revealing no differences between the groups (Table 4).

The HP group's lactate concentration measured directly after arrival on ICU was highly significantly lower (Fig. 2). The difference is smaller between the groups after 4 h while remaining statistically significant. We observed normal values and no inter-group differences in lactate concentrations after 24 h. All other laboratory results and values from the blood–gas analysis reflect a stable postoperative course and no significant inter-group difference (Table 5).

Table 3. Postoperative clinical outcome.

| Variables | LP group (48 patients) | HP group (44 patients) | *p*-value |
|---|---|---|---|
| Mortality | 0 (0%) | 0 (0%) | 1.00 |
| Thromboembolic events | 2 (4%) | 1 (2%) | 1.00 |
| HIT | 0 (0%) | 0 (0%) | 1.00 |
| SIRS | 0 (0%) | 0 (0%) | 1.00 |
| Pneumonia | 1 (2%) | 0 (0%) | 1.00 |
| Seizure | 1 (2%) | 0 (0%) | 1.00 |
| Superficial wound infection | 2 (4%) | 3 (7%) | 0.67 |
| Pleural effusion | 16 (33%) | 21 (48%) | 0.20 |
| Pericardial effusion | 3 (6%) | 4 (9%) | 0.71 |
| Tachycardia | 5 (10%) | 6 (14%) | 0.75 |
| Atrial fibrillation | 9 (19%) | 16 (36%) | 0.065 |
| Ventricular fibrillation | 1 (2%) | 0 (0%) | 1.00 |
| Reintubation | 2 (4%) | 1 (2%) | 1.00 |
| Pneumothorax | 4 (8%) | 5 (11%) | 0.73 |
| Acute renal failure | 1 (2%) | 0 (0%) | 1.00 |
| Bleeding requiring reoperation | 1 (2%) | 3 (7%) | 0.34 |
| Total number of complications | 42 | 52 | 0.34 |
| Required RBC units | 1.5 ± 2.2 | 1.7 ± 2.2 | 0.62 |
| Required fresh frozen plasma | 0.7 ± 1.3 | 0.5 ± 1.1 | 0.37 |
| Required thrombocyte concentrate | 0.3 ± 0.7 | 0.2 ± 0.5 | 0.31 |
| Required blood products | 24 (50%) | 31 (70%) | 0.056 |
| Cessation of catecholamine support [h] | 26.0 ± 45.9 | 13.8 ± 24.8 | 0.12 |
| Ventilation time [h] | 11.9 ± 5.6 | 10.3 ± 5.0 | 0.15 |
| ICU and intermediate care stay [days] | 4.0 ± 3.9 | 3.2 ± 2.4 | 0.23 |
| Total LOS [days] | 12.2 ± 8.1 | 12.6 ± 6.9 | 0.79 |

Mortality: 30-day mortality, HIT: heparin-induced thrombocytopenia, SIRS: systemic inflammatory reaction syndrome, RBC: red blood cell, ICU: intensive care unit, LOS: length of stay.

Table 4. Postoperative hemodynamic assessment.

| Variables | LP group (48 patients) | HP group (44 patients) | *p*-value |
|---|---|---|---|
| Cardiac index [l min $m^{-2}$] | | | |
| First measurement | 2.6 ± 0.8 | 2.4 ± 0.5 | 0.12 |
| After 4 h | 2.7 ± 0.5 | 2.9 ± 0.7 | 0.16 |
| After 24 h | 2.8 ± 0.5 | 3.0 ± 0.7 | 0.15 |
| MAP [mmHg] | | | |
| First measurement | 85 ± 14 | 90 ± 17 | 0.12 |
| After 4 h | 79 ± 12 | 75 ± 10 | 0.18 |
| After 24 h | 76 ± 10 | 77 ± 11 | 0.78 |
| CVP [mmHg] | | | |
| First measurement | 10.4 ± 5.0 | 10.7 ± 4.3 | 0.67 |
| After 4 h | 8.8 ± 3.7 | 10.0 ± 3.3 | 0.12 |
| After 24 h | 10.4 ± 4.5 | 10.1 ± 4.7 | 0.81 |
| SVR [dyn s $cm^{-5}$] | | | |
| First measurement | 1250 ± 448 | 1383 ± 484 | 0.21 |
| After 4 h | 1030 ± 345 | 1016 ± 254 | 0.85 |
| After 24 h | 1058 ± 356 | 974 ± 211 | 0.22 |
| PCWP [mmHg] | | | |
| First measurement | 12.8 ± 4.7 | 12.6 ± 5.5 | 0.86 |
| After 4 h | 12.4 ± 4.8 | 11.7 ± 5.9 | 0.65 |
| After 24 h | 12.3 ± 3.4 | 12.0 ± 5.2 | 0.81 |
| PVR [mmHg] | | | |
| First measurement | 179 ± 110 | 175 ± 74 | 0.85 |
| After 4 h | 161 ± 134 | 184 ± 84 | 0.51 |
| After 24 h | 150 ± 73 | 173 ± 80 | 0.19 |
| HR [1 $min^{-1}$] | | | |
| First measurement | 86 ± 13 | 82 ± 11 | 0.068 |
| After 4 h | 87 ± 16 | 84 ± 12 | 0.26 |
| After 24 h | 85 ± 13 | 87 ± 14 | 0.46 |

MAP: mean arterial pressure, CVP: central venous pressure, SVR: systemic vascular resistance, PCWP: pulmonary capillary wedge pressure, PVR: pulmonary vascular resistance, HR: heart rate.

### 3.4. Comparison of patients with and without delirium

We compared the six patients, who experienced a delirium, to the group of all other patients. Table 6 highlights these patients' most relevant clinical parameters. Those

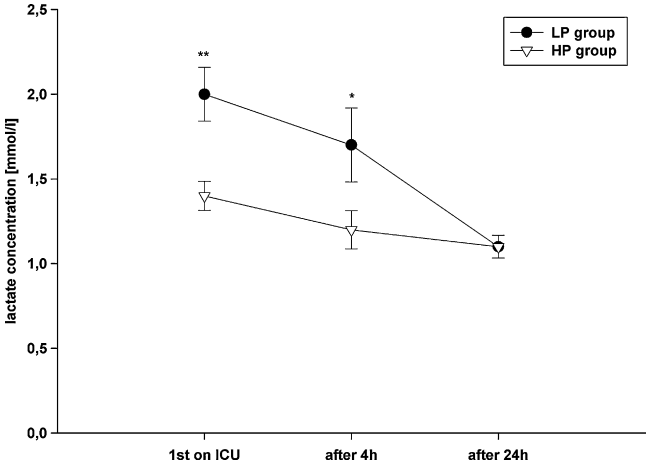


Fig. 2. Postoperative lactate concentration over the time on the intensive care unit. Note that the LP group's lactate rises significantly immediately after surgery (*$p < 0.05$ and **$p < 0.001$ between the groups, error bars indicate standard error of the mean).

Table 5. Postoperative blood gases and laboratory results.

| Variables | LP group (48 patients) | HP group (44 patients) | *p*-value |
|---|---|---|---|
| Lactate [mmol $l^{-1}$] | | | |
| First measurement on ICU | 2.0 ± 1.1 | 1.4 ± 0.6 | <0.001 |
| After 4 h | 1.7 ± 1.5 | 1.2 ± 0.7 | 0.047 |
| After 24 h | 1.1 ± 0.5 | 1.1 ± 0.4 | 0.80 |
| $PaO_2$ [mmHg] | | | |
| First measurement on ICU | 317 ± 100 | 359 ± 120 | 0.076 |
| After 4 h | 122 ± 45 | 122 ± 28 | 0.99 |
| After 24 h | 100 ± 29 | 102 ± 30 | 0.83 |
| $PaCO_2$ [mmHg] | | | |
| First measurement on ICU | 40.8 ± 6.1 | 41.2 ± 6.5 | 0.77 |
| After 4 h | 40.7 ± 4.9 | 40.1 ± 4.6 | 0.61 |
| After 24 h | 40.2 ± 4.1 | 39.2 ± 4.0 | 0.27 |
| Hemoglobin concentration [g $dl^{-1}$] | | | |
| Preoperative | 14.2 ± 1.5 | 13.9 ± 1.7 | 0.34 |
| 1st po day | 10.1 ± 1.3 | 10.0 ± 1.2 | 0.68 |
| 2nd po day | 9.8 ± 1.2 | 9.8 ± 1.1 | 0.98 |
| 7th po day | 10.3 ± 1.6 | 10.3 ± 1.3 | 0.96 |
| Lowest measured value | 9.0 ± 1.2 | 8.8 ± 1.0 | 0.22 |
| C-reactive protein [mg $l^{-1}$] | | | |
| Preoperative | 8 ± 9 | 10 ± 18 | 0.58 |
| 1st po day | 63 ± 16 | 85 ± 37 | 0.088 |
| 2nd po day | 202 ± 90 | 206 ± 66 | 0.87 |
| 7th po day | 101 ± 69 | 101 ± 51 | 0.98 |
| Highest measured value | 162 ± 101 | 192 ± 96 | 0.16 |
| CK–MB [U $l^{-1}$] | | | |
| Preoperative | 13.8 ± 8.0 | 14.8 ± 11.0 | 0.77 |
| 1st po day | 50.3 ± 29.7 | 48.2 ± 49,5 | 0.81 |
| 2nd po day | 29.7 ± 18.1 | 25.9 ± 15.9 | 0.33 |
| 7th po day | 22.5 ± 23.2 | 22.8 ± 27.8 | 0.97 |
| Highest measured value | 71.3 ± 35.8 | 67.3 ± 47.6 | 0.65 |
| Creatinine [mg $dl^{-1}$] | | | |
| Preoperative | 1.08 ± 0.7 | 1.05 ± 0.3 | 0.76 |
| 1st po day | 0.99 ± 0.5 | 0.94 ± 0.3 | 0.60 |
| 2nd po day | 1.07 ± 0.8 | 1.01 ± 0.3 | 0.62 |
| 7th po day | 1.05 ± 0.5 | 1.11 ± 0.5 | 0.58 |
| Highest measured value | 1.30 ± 0.0 | 1.29 ± 0.5 | 0.98 |
| Urine output | | | |
| First 24 h [ml] | 1774 ± 600 | 1649 ± 509 | 0.23 |

$PaO_2$: arterial partial pressure of oxygen, $PaCO_2$: arterial partial pressure of carbon dioxide, CK–MB: creatine kinase MB.

with delirium were slightly older and had longer CPB runs without reaching statistical significance. The affected patients were ventilated significantly longer and were slightly longer on the ICU as well (Table 6). Interestingly, patients with delirium had a lower MAP measured 24 h postoperatively than those without delirium (68.6 ± 6.5 vs 77.2 ± 10.9 mmHg, $p < 0.001$). None of the other preoperative parameters or those concerning postoperative function and complications revealed any significant differences between the small cohort of patients with delirium and the rest of the study population.

## 4. Discussion

The future of coronary revascularization has been conceived according to two new strategies: interventional treatment using stents and off-pump surgery for selected patients. However, recent evidence speaks a different language: the Syntax trial has led clinicians to conclude that the percutaneous approach (even using drug-eluting stents) for three-vessel disease and main-stem stenosis is not superior to CABG in the short run, and that it might cause more complications in long-term follow-up [10,11]. Thus, cardiologists and cardiac surgeons have recently stated that surgical revascularization is the only evidently appropriate treatment for this condition [12]. Off-pump coronary surgery for surgical revascularization has gained much attention during the past decade. However, outcome analyses have ultimately shown no clear benefit; in fact, off-pump surgery may even be inferior to on-pump revascularization in most hands [13].

In addition to mortality as the paramount outcome parameter, there are other major problems concerning morbidity in association with on-pump CABG [14]. Cognitive dysfunction and postoperative delirium are among the most disturbing complications observed after coronary surgery. These are frequently attributed to CPB. Inflammation and clinically evident capillary leak syndrome are considered to play major roles [15]. However, in our study, we observed no difference in weight gain (as a parameter of systemic involvement of capillary leak syndrome) between the study groups, nor did weight gain differ between patients with and without delirium. However, the possibility of damage to the blood–brain barrier by inflammation caused by CPB cannot be excluded. One factor arguing against inflammation as the main reason for cognitive dysfunction is that the frequency of delirium has been the same in off-pump surgery in a variety of studies [16–18].

Both inflammation and the creation of microemboli have often been considered to play a major role in postoperative cognitive dysfunction. There is evidence that each manipulation by the perfusionist results in a greater microembolic burden [19]. Some authors have speculated that these

Table 6. Comparison of patients with delirium and patients without delirium from the entire study population.

| Variables | Patients with delirium (6 patients) | Patients without delirium (86 patients) | *p*-value |
|---|---|---|---|
| Age [years] | 72.7 ± 5.6 | 66.5 ± 9.2 | 0.11 |
| CPB time [min] | 115 ± 21 | 95 ± 28 | 0.067 |
| Total number of complications | 6 | 102 | 0.78 |
| Cessation of catecholamine support [h] | 56 ± 53 | 18 ± 36 | 0.028 |
| Ventilation time [h] | 16.7 ± 9.4 | 10.7 ± 4.8 | 0.008 |
| ICU and intermediate care stay [days] | 5.0 ± 2.7 | 3.5 ± 3.3 | 0.29 |
| Total LOS [days] | 12.0 ± 2.0 | 10.7 ± 4.8 | 0.89 |
| First lactate [mmol $l^{-1}$] | 2.3 ± 1.7 | 1.6 ± 0.9 | 0.13 |
| MAP after 24 h [mmHg] | 69 ± 7 | 77 ± 11 | <0.001 |
| Highest creatinine [mg $dl^{-1}$] | 1.28 ± 0.3 | 1.29 ± 0.8 | 0.96 |

CPB: cardiopulmonary bypass, ICU: intensive care unit, LOS: length of stay, MAP: mean arterial pressure.

microemboli account for early cognitive dysfunction [3,4], while others found no correlation between microemboli and delirium [18,20].

Our hypothesis of regional cerebral hypoperfusion during low-pressure phases as the main reason for early postoperative deficits is based on our present findings. Further, recent studies on pulmonary impairment following CPB point in the same direction. Pulmonary impairment after CPB has often been attributed to result from inflammation. We were able to prove that regional lung ischemia is a main reason for the impairment and can be counteracted by pulmonary perfusion during CPB [21]. Adding pulsatility to pulmonary perfusion additionally reduced the inflammatory reaction, which is another indication for the regional hypoperfusion hypothesis [7]. While all patients on CPB may encounter such regional pulmonary hypoperfusion, not all of them develop the most severe clinical manifestation of acute respiratory distress syndrome. The same may apply to early postoperative cognitive dysfunction, as all patients on CPB may experience regional cerebral hypoperfusion during low-pressure perfusion, but all will not develop a delirium. Global cerebral perfusion seems to be not different between the groups, as near-infrared spectroscopy (NIRS) and other parameters did not differ. The regional perfusion distribution might not always reflect the demands according to our findings. The factors, why some patients are affected with delirium and others not, are still not identified. In future, better regional perfusion diagnostic features might be available to confirm our hypothesis of regional malperfusion.

It might be possible that hypothermic CPB can protect against this pressure-dependent regional hypoperfusion; but this needs to be answered in a separate study, as all patients in this trial received normothermic perfusion.

A very rough marker of hypoperfusion in the setting of maintained liver function is arterial lactate concentration. We noted significantly elevated lactate levels in the LP group as an indication of insufficient organ perfusion. It has been shown that even slightly elevated lactate levels are predictors of a higher rate of complications [22,23]. We did not observe more complications in the group with higher postoperative lactate concentrations — but our study was not designed for this end point, nor was our cohort size large enough to statistically answer that question.

A longer CPB run has been found to result in elevated lactate concentrations as well [24,25]. In this study, we noticed slightly higher CPB times in the LP group without reaching statistical significance. The longer CPB duration in our cohort did not correlate with neuropsychological outcome; thus, it may well not be the main reason for the cognitive impairment.

We searched thoroughly for any side effects of higher perfusion pressure in this study. Before initiating the study, we specifically suspected bleeding and hemodynamic changes due to elevated use of vasoconstrictors as possible consequences. However, we did not identify more bleeding complications, or lower hemoglobin levels in the HP group. Further, systemic and pulmonary vascular resistance in the postoperative period did not differ between the groups, nor did any other hemodynamical parameter. Other postoperative clinical parameters such as kidney function, pulmonary function, and inflammatory reaction were not different between the groups. The slightly longer ventilation times and stay on the ICU in the LP group might be due to that group's high incidence of delirium. However, this difference was not statistically significant, and our study was again not powered to study differences in this end point. The 12.5% incidence of delirium is worrisome and may, in a larger cohort of patients, also correlate with other complications such as sternum instability or pulmonary complications.

The comparison of patients with or without delirium revealed surprisingly that patients with delirium were not significantly, but only slightly older than those without delirium. Age has been mentioned as the most relevant risk factor for postoperative cognitive dysfunction [1,2]. A major limitation of this subgroup analysis is the very low number of patients in one group (6 vs 86 patients), and the study was not powered to identify risk factors. Therefore, it would be inappropriate to discount age as a contributing factor only because age did not significantly differ between our groups with or without delirium in this study. The same limitation may explain why the length of hospital stay in the cohort of patients with and without delirium did not statistically differ. However, perfusion pressure may, in fact, be a key component in the etiology of this disorder, as we noticed significant lower postoperative MAP in the group with delirium compared with the group without delirium.

One limitation of this study is its small sample size and single-center nature. The patient numbers in this investigation allowed us to address cognitive dysfunction as the primary end point. Additional clinical end points could be studied in a different setup with more patients and several centers.

The main limitation of the present study is that the study analysis was not performed according to the intention-to-treat but rather according to the per-protocol principle. Our future larger trial on the perfusion pressure will also analyze the dropout patients in an intention-to-treat analysis. Still, we cannot rule out the potential of a bias in our data, as there could be a relationship between the inability to achieve high perfusion pressure (like in five of our randomized patients) and those presenting early cognitive deficit. While a concrete MMSE is not available in the five patients in whom the target pressure could not be achieved, we have noticed no delirium in these patients and can rule out a bias on this end point.

Furthermore, we only investigated cognitive state at one postoperative time point. This might not suffice to conclude that cognitive dysfunction is transient, not permanent. However, although we did not repeat the MMSE, the delirium in all patients resolved before discharge. In the planned multicenter trial, we will not only focus on early cognitive dysfunction but also concentrate on the long-term cognitive outcome of these patients.

In conclusion, in this single-center, randomized study, we found that maintaining mean perfusion pressure during normothermic CPB at physiological values (80—90 mmHg) is associated with less early cognitive dysfunction and delirium after CABG. Elevated perfusion pressure is not associated with increased morbidity and mortality. A larger multicentric trial should investigate this CPB modification and should also focus on the midterm fate of the cognitive outcome.

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## Appendix A. Conference discussion

***Mr J. Pepper*** (*London, United Kingdom*): This is a very well-conducted, prospective, single center, randomized controlled trial. The most surprising feature to me was that on the basis of cognitive outcome using the mini mental stress test as the primary endpoint, out of only 44 versus 48 patients, the authors were able to report a significant difference. Usually you need much larger numbers. So that surprised me.

But I have a few questions. And forgive me, I may have missed this in the presentation. But no details seem to be given of any preoperative carotid studies. Such studies are important not only for the information about the carotid arteries themselves, but as a marker for severe atherosclerosis in the thoracic aorta. Perhaps you'd like to comment.

A few more questions. The extracorporeal perfusion was carefully conducted with flows of 2.6 l $min^{-1}$ in both the high and low pressure groups. I assume the prime volume was consistent, and which arterial filters were used?

You used near-infrared spectroscopy, but this can be a difficult technique as it is dependent on hemoglobin, on pressure, on flow, on carbon dioxide levels. Perhaps you would comment on that.

Tests of cognitive function themselves are difficult to apply, and I'd like to know who carried out these and were they repeated later, that is to say, at 6 months perhaps, postoperatively?

The incidence of delirium, 6 out of 48, does seem a little bit high. So I would like to know what is your definition of delirium?

And finally, do you intend this to be a pilot study for a larger multicenter trial, perhaps, in which patients with a history of cerebral vascular disease are not excluded?

***Dr Siepe***: The exclusion criteria of not putting patients with cerebral vascular disease into the study, was based on the fact that we did not want to put those patients at harm of this high blood pressure. It's our institutional protocol to keep the blood pressure in those patients well above the level of 70 throughout the whole pump run.

For the delirium definition, we defined for this study that a difference of 10 points, together with a positive assessment of a psychologist, is referred to as delirium. The observers for the study were two people trained to do the mini mental tests, who independent and blinded.

You mentioned that in this small group of patients we were able to prove a significant difference, and that is mainly because of the 6 patients with a very marked decline. You saw that in the group of low pressure perfusion, the standard deviation was higher and this was because of those patients with the very marked reduction.

You asked about the missing cerebral perfusion measurements and the reasons for that. We were trying to add a Doppler analysis of the flow through the carotids to our study. We only managed it in some patients, but we saw no influence of regulating the pressure up and down on our measurement of the carotid flow. Also we were not able to do this in all the patients.

Regarding the NIRS measurement, as you correctly mentioned, the influences on the value reached by this monitoring tool are various, and it was not surprising that we could not see any difference between left and right, or between the groups, because of the huge amount of influences. For this value and most of the other outcome parameters, the study would have been needed many more patients in the power analysis.

***Mr Pepper***: I must say that in my own practice I keep the mean pressure the same as the age of the patient and I find that's quite a good marker.

***Dr Siepe***: That's good for the older ones but not for the congenital cases, I guess.

***Dr Beyersdorf***: I might also add that the observation that the delirium, which it is often said, is related to cardiopulmonary bypass, seems not to be true. We see it in off-pump coronary surgery, we see it in trauma surgery, and infarct patients also get it. So obviously all those patients who get it otherwise, are those who have a low blood pressure for whatever reason — trauma, infarction, lifting the heart during off-pump surgery. So that was the start of that study. And I was, as you are, very surprised that with only 44 versus 48 patients we already saw a difference. I mean I can't explain it, but that's how it is.