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Article type : Clinical investigation

Serum-neuroproteins, near-infrared spectroscopy, and cognitive outcome after beach-chair shoulder surgery: observational cohort study analyses

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Short running title: Neuroproteins, near-infrared spectroscopy and cognitive outcome

A word count (excl. abstract and references) 3787 incl. explanatory texts.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/AAS.13691

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Conflicts of interest

This study was funded in part a limited unconditional research grant from Central Region Denmark (TK). TK and JRL have received minor honoraria for lectures and advisory boards from Covidien/Medtronic. HZ is a co-founder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg, has served at scientific advisory boards for Roche Diagnostics and Eli Lilly and has received travel support from TEVA. There are no patents, products in development or marketed products to declare. This does not alter our adherence to all the AAS policies on sharing data and materials.

Abstract

Background: Cerebral hypoxia may occur during surgery but currently used cerebral oxygenation saturation (rSO2) monitors remain controversial with respect to improving clinical outcome. Novel neuroprotein biomarkers are potentially released into systemic circulation and combined with near-infrared spectroscopy (NIRS) could clarify the presence of per-operative cerebral hypoxia. We investigated changes to serum-neuroprotein concentrations postsurgically, paired with NIRS and cognitive outcome, in patients operated in the beach chair position (BCP).

Methods: A prospective cohort in 28 shoulder surgery patients placed in the BCP. Blood samples were collected before induction of anaesthesia, and 2 hours and 3-5 days postoperatively. We analysed blood-levels of biomarkers including tau and neurofilament light (NFL). We *post hoc* assessed the cross-wise relationship between biomarker levels and postsurgical changes in cognitive function and intraoperatively monitored rSO2 from NIRS.

Results: Serum-NFL decreased from 24.2 pg/mL to 21.5 (P=0.02) 2 hours postoperatively, then increased to 27.7 pg/mL on day 3-5 (P=0.03). Conversely, *s*-tau increased from 0.77 pg/mL to 0.98 (2 h), then decreased to 0.81 on day 3-5 (P=0.08). In 14/28 patients, episodic rSO2 below 55% occurred, and the duration <55% was correlated to change in s-tau (P<0.05). The cognitive function z-score at 1 week and 3 mo. correlated to the change in tau (P=0.01), but not to NFL.

Conclusion: Some biomarkers were significantly changed with surgery in the beach chair position. The change was at some points associated to postoperative cognitive decline, and to intraoperative low rSO2. (237)

Keywords: tau protein; neurofilament light chain; near-infrared spectroscopy; cerebral hypoxia; beach chair position; postoperative cognitive dysfunction

Editorial Comment:

While the beach chair position may be popular for surgical convenience in shoulder surgery, it may be at times unfavorable for patients and head-neck circulation. In this study of participants undergoing shoulder surgery in the beach chair position, the authors followed intraoperative cerebral oxygenation and also found some changes in post-operative biomarkers which could indicate cerebral injury. Post-operative cognitive dysfunction assessment also showed signs of injury in some participants.

Introduction

Recent reports have indicated that *post hoc* measurement of neuroprotein markers, that are released into the systemic circulation subsequent to central neuraxis injury, may be relevant to predicting long-term injury and adverse neurologic outcome. Novel candidate biomarkers *tau* [1] and Neurofilament Light chain (NFL) [2-4] in blood samples could thus be used to determine the hypothetical existence of cerebral hypoperfusion with subsequent neuraxonal injury. Standard ELISAs for total tau (T-tau) have been transferred onto the Single molecule array (Simoa) platform, which allows for the ultrasensitive measurement. Plasma T-tau concentrations correlate poorly with CSF, but in acute hypoxic brain injury [1], a biphasic release of tau into the bloodstream was observed with a first peak occurring during the first few hours postinjury and a second broad peak occurring after a few more days; these increases were predictive of outcome. In a study on concussed professional ice hockey players [4], plasma T-tau concentration at 1-hour post-injury was increased compared with preseason concentrations and predicted return-to-play time with high accuracy. In another study of 34 patients with varying degree of traumatic brain injury (TBI) [6], plasma tau concentrations in samples collected within 24 hours post-injury showed high accuracy to differentiate complicated mild TBI from controls (area under the curve 0.901). Olivera et al. have reported increased mean plasma tau concentration in military personnel with a history of self-reported TBI compared with controls without such a history [5]. Additionally, post-concussive symptoms correlated with plasma tau concentration in the TBI group, suggesting that the increase, although variable, could be of pathophysiological relevance. The half-life of tau is much shorter (hours) in plasma than in CSF (weeks). [1-6] We speculated that, irrespective of the nature of the injury (trauma or hypoxia), tau and NFL could be detected in blood, hypothesizing that these could help establish a perspective on the response to suspected low regional cerebral saturation (rSO_2) in risk patients, signifying a first response to cell injury.

Cerebral oxygen monitors

Brain resilience to oxygen deprivation is today poorly understood, especially in circumstances where clinical function cannot be monitored, e.g. during general anaesthesia. Preservation of cerebral perfusion and oxygenation during anaesthesia and surgery is essential to normal postoperative brain function [7,11]. Although no ideal cerebral monitor as yet exists, currently used devices in high-risk patients and in risk surgery include continuous rSO_2-level monitoring with scalp penetrating near-infrared spectroscopy (NIRS) [8,9], transcranial Doppler [10], which allow the detection, and thus avoidance of, cerebral hypoperfusion. The restriction to both of these methods is that neither as yet has a validated pre-defined cut-off level below which neuraxial injury is predictable and clinical neurologic outcome is affected. Monitoring devices like NIRS are routinely used during cardiopulmonary bypass [11] and at times for surgery in the beach chair

position (=BCP, sitting upright) [12]. This position is well-known to physiologically challenge cerebral blood flow regulation in conjunction with general anaesthesia [13]. However, clinical trials have yet to consistently demonstrate perioperative stroke risk-reduction from these technologies [7].

Currently, the incidence of perioperative ischemic stroke in non-cardiac, non-neurological, and non-major vascular surgery is 0.1%-1.9%, depending on associated risk factors [14,15] but covert stroke and TCI are more frequent, possibly as high as 10% [16]. Certain factors are associated with increased risk, i.e. the type of surgery, patient positioning and comorbidity. Reports of stroke related to BCP patients (e.g. shoulder arthroscopy)[12] may be indicative that cerebrovascular hypoxia occurs subsequent to low brain perfusion pressure [1].

This primary objective of this study was to observe longitudinal postsurgical changes to serum neuroprotein concentrations (NFL, tau, Abeta40 [17], Abeta42), in association with concurrent peroperative changes to regional cerebral oxy-saturation, and to postoperative cognitive function (by so-called ISPOCD tests [18]) which might arise from low cerebral perfusion states in the beach chair position. Therefore, shoulder surgery patients were targeted. Secondly, the aim was to statistically explore a possible NIRS threshold if possible. The hypothesis was that low rSO2 might be associated with biomarker detection (if any) and that there could be a mutual association to postoperative cognitive decline (POCD), indicating clinical relevance. A further hypothesis was that a threshold rSO2 level could be determined that would allow prediction of adverse neurologic outcome.

Methods

Subjects

This was a prospective observational study. The study complies with the STROBE statement of reporting guidelines [19]. The investigation and data management complied with legal guidelines (Helsinki declaration) and was approved by the regional research ethics committee (RegionMidt Research Office; ref.nr. 614870, case number 1-16-02-336-15 (date of approval 27-08-2015). Eligible patients were adult ASA Physical Status I and II patients scheduled for shoulder surgery in general anaesthesia in the BCP. Since it was a noninterventional trial, no clinical trial registry took place. All patients signed informed consent.

The study had first been designed as a case-control study and the group size was calculated to 14 which assumed 25% of patients would develop rSO2-decrease >25% from baseline, and that NIRS could reduce this proportion to 0% in an intervention group, based on the manufacturer's report from clinical observations. In advance, this was changed to an observational cohort to prioritize further insight into novel biomarkers and retain the group size (2 x groups, n=28).

Monitoring and anaesthesia

In patients requiring major shoulder surgery (e.g. Rotator cuff repair or open surgery), analgesia was provided with preoperative ultrasound-guided Interscalene nerve block injection of 7-10 ml 0.5% bupivacaine with adrenaline vasoconstrictor plus 4 mg Dexamethasone, applied perineurally.

A radial artery line was inserted to monitor blood pressure (MAP), to collect study samples, and for blood-gas (pH, CO_2) analysis (ABL90 Flex plus®, Radiometer, Copenhagen). MAP was calibrated at heart level and used to guide anaesthetic management, which consisted of maintaining MAP≥70 mm Hg with iv ephedrine 5 mg bolus or fluid bolus to achieve this target. Monitoring of ECG, pulse oximetry, spirometry, capnometry was standard. All patients received total intravenous (TIVA) general anaesthesia with propofol induction (0.5-1 mg/kg), continuous propofol maintenance (25-75 mcg/kg/min) and remifentanil infusion (0.25-0.5 mcg/kg/min), tracheal intubation and controlled ventilation with fiO2 0.35-0.40. Normocapnia (4.6-5.1 kPa ET-CO2) was ensured.

Biomarkers

Blood samples were collected from the arterial line at baseline (0) prior to anaesthesia induction and drawn into tubes. The samples were collected at 0, 2 hours, and 3-5 days postoperatively, coinciding with a scheduled visit. Biomarker samples were centrifuged and stored at -20˚C for later analysis. NFL concentration was measured using an in-house assay by single molecule array (Simoa), as previously described [20]. Total tau (T-tau), Abeta42 and Abeta40 concentrations were measured by Simoa technology using a commercially available total-tau kit (Quanterix, Billerica, MA, USA), as previously described [21]. All measurement analyses were performed in one round of experiments using one batch of reagents with baseline and follow-up samples from the same individual analysed next to each other by board-certified laboratory technicians who were blinded to clinical data.

NIRS

Prior to anaesthesia, continuous NIRS-monitoring was established (INVOS®, Covidien, Finland) via bifrontal cutaneous self-adhesive pads on cleansed skin on the forehead. The rSO_2-readout was via screen display and trend curve, and data were collected for *post hoc* analysis using dedicated software (Medtronic, MN, USA). The NIRS screen was unblinded to both anaesthetist and investigator, but rSO_2 values did not prescribe the behaviour of the attending anaesthetist.

NIRS-data was collected as individual bifrontal digital rSO_2-curves and analysed using dedicated software. Briefly, rSO_2 trend curves (Fig. 3) were analysed by difference from baseline value and characterized

according to %rSO_2, and duration (min) at particular levels. This allowed individual correlation analyses from rSO_2 to biomarkers and cognitive function outcomes.

Assessment of POCD

Cognitive outcome was tested individually before, 1 week and 3 months after surgery, by the ISPOCD [18] test battery, and z-scores were calculated to express change in cognitive performance. We used the International Study of Postoperative Cognitive Dysfunction (ISPOCD) test battery, including the Visual Verbal Learning test, the Concept Shifting test, the Stroop Colour Word Interference test, and the Letter Digit Coding test with seven variables. The change from the preoperative to the postoperative test was calculated in each patient and we corrected for the practice effect by subtracting the average change in healthy controls. A Z-score was then obtained for each variable by dividing by the standard deviation of the control group's change in performance so a positive Z-score indicated a deterioration in performance. A composite Z-score was calculated as the sum of the seven Z-scores divided by the SD of the control group's sum of Z-scores. Patients had POCD when either two out of seven individual Z-scores exceeded 1.96 or the composite Z-score exceeded 1.96.

Statistical analysis

All data were tested for normal distribution. We used MedCalc Statistical Software version 19.0.7 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019). Biomarker samples (NFL, tau) were compared by rank sum test (Wilcoxon paired sample) before (baseline, BL) and after surgery (2 hour and day 3-5). In order to examine the putative relationships between rSO_2-threshold and biomarkers, including *depth* and duration, rSO_2 profile curves were summarized as duration (minutes) at predefined rSO2-levels (I. e. 40-55%, and relative decline (25 and 30% from baseline). The summarized measures were then tested for correlation (sum of least squares) to each biomarker and the correlation between these markers and the cognitive z-score was assessed. Many cross-wise correlations could thus be performed, and only the positive correlations are reported here. Further, no statistical corrections were performed for multiplicity in testing (e.g. Bonferroni), since typically only 3-4 tests were required for each parameter cross-testing.

Results

We included 28 patients aged 56.1 yr (mean) from November 2015 to April 2016. A presentation of patient characteristics is given in table 1. Surgery duration was typically in the range of 75 - 90 min. [Table 1.]

Biomarkers

Intra-assay coefficients of variation were 6.2% for NFL and 13.2% for tau.

Participants' blood sample neuroproteins tau and NFL were significantly increased in serum after surgery and anaesthesia in the beach chair position, but with different time profiles (Fig. 1, Table 1). D'Agostino-Pearson test showed tau, but not NFL, to follow a normal distribution, with one baseline NFL outlier value (Grubbs, left-sided: 75 vs. mean 24.2 pg/mL) detected. The outlier was however included in the further analysis for the sake of robustness, in spite of this lowering the significance levels (from 0.008 to 0.03).

s-NFL decreased from baseline to 2 hr postop (P=0.03), then increased by day 3-5 (P=0.03) postoperatively. Conversely, tau level significantly decreased on day 3-5 (P=0.04) (Fig.1). Abeta40 and Abeta42 were unchanged (Table 1).

To validate the hypothetical association intra-neuroprotein, dispelling a random effect, the relative peak changes in biomarkers were compared (N=27) by linear regression analysis (sum of least squares), revealing a significant association between the changes in tau and NFL levels (P=0.035) (Fig. 2).

NIRS

rSO2 before anaesthesia induction was 67.8 (mean; median 67.5), (65-70: 95CI) %OxyHgB saturation (N=28). A typical rSO2-curve with description is shown in Fig.3.

After anaesthesia induction, rSO2 values briefly increased above baseline in all patients, from elevated oxygen content at intubation time, and subsequently decreased when patients were positioned upright in the BCP and inspired oxygen content was reduced (Fig. 3).

An rSO2-value that decreased >25% relative to BL was seen in all (28/28) patients, but in 14 of 28 patients, the value decreased to less than 40% of baseline (or, 55% in absolute figures) as shown in Fig. 4.

The duration time (min) of exposure to low rSO2 (≤55%) was found to correlate with the change in tau (P=0.048) (Fig. 5).

Cognitive Outcomes

No patient suffered from Serious Adverse Events (SAE, e.g. stroke) nor had any postoperative signs of clinical neurologic deficit, nor delirium. However, postoperative cognitive dysfunction was detected by the ISPOCD test battery in 1 out of 25 patients (4%) (3 patients did not complete 3-month testing) at each postoperative test session.

Individual ISPOCD z-scores were compared to biomarkers (linear regression), and whilst there was no association to NFL (P=0.3), there was an association between tau change at 2 hours postoperative and 3-month POCD (P=0.01) (Fig. 6). We found no significant associations between day 3-5 (tau, nor NFL), and z-scores. Tau change (2 h) was +18% (mean) and was associated with 3-month z-scores.

Discussion

In this observational cohort, neuroprotein blood-levels of NFL and tau were found to increase significantly after shoulder surgery in BCP. Concomitant peroperatively recorded decreases in (frontal lobe) cerebral haemoglobin oxygen saturation (rSO2) were significantly correlated to the biomarkers, specifically, s-tau was correlated to low rSO2, measured with near-infrared spectroscopy (NIRS) in the frontal lobes.

A possible explanation for the observed phenomenon could be an indication that minimal, yet detectable, neuronal cell debris is released into systemic blood as a result of regional cerebral desaturation, which was in turn detectable by NIRS. Along that line, it has previously been reported that cerebrospinal fluid (CSF) transaminases (SGOT, ALAT) were elevated in hypotensive anaesthesia (≤50 mmHg) [23, 24]. In non-human studies, Maas [25] reported that CSF enzymes were elevated in acute brain injury in rats. Also, the relationship between low blood pressure and tau protein is recognized in Alzheimer's Disease [26].

Brain hypoxia can also lead to irreversible damage, but the extent of cerebral desaturation /ischemia required to elicit neurological deficits postoperatively remains unidentifiable. This renders an obstacle to the implementation of clinical guidelines. In patients undergoing surgery in the beach chair position, neuronal injury could manifest itself as measurable decline in neuropsychological test performance relative to preoperative levels (POCD). Anoxic neuronal injury typically results in attention deficit and lower processing speeds, which can be detected down to millisecond deficits by test batteries [18]. POCD has been defined in several different ways, but few have examined POCD subsequent to surgery in BCP, complicating the evaluation of clinical impact of cerebral desaturation. Here, we found relatively little evidence to suggest POCD, although two patients did exhibit this, one after a week, the other after 3 months. The standard ISPOCD battery is likely not be sufficiently sensitive to detect minimal or diffuse neuronal injury, and may not be reflective of such small increases in biomarkers that our data showed. Patients with manifest neurologic incumbencies who *were* exposed to low rSO_2 during cardiopulmonary bypass (CPB) [11, 22] could potentially have elevated biomarkers, but the CPB wash-out effect could obliterate such results. Similarly, POCD incidence was not different in CPB patients grouped according to rSO2 profile (high- vs. low saturation), presumably because all patients had equal microcirculatory shortcomings undifferentiated by NIRS. [27]. Our data reveals, perhaps merely an indication, that a previously unreported significant association between tau elevation and POCD z-scores, exists.

Novel, sensitive neuromarkers tau, NFL (and SNTF) have previously been reported to be affected by minimal traumatic brain injury and radiation, and their release into plasma is independent of blood brain barrier integrity [28]. Recently both tau and NFL have been reported to be sensitive biomarkers for neuronal injury post-surgery (CAPACITY and ARCADIAN studies) [29]. It was reported that while both markers were elevated postsurgically in two unselected cohorts, tau and NFL were measured in plasma, and tau was

maximally elevated (up to 3-fold) 6 h post surgery. NFL increased by 47% (mean) but remained elevated for longer. Moreover, our results tentatively reveal a stronger association between tau and POCD, than NFL and POCD. Taken together, these findings corroborate our results and suggest which path to take in future discovery of time-depth ischemia similar to troponins and myocardial ischemia. Abeta was found uninterrupted in the current study, and is perhaps better linked to vascular injury and a more chronic marker [29].

This was an exploratory study, with the only predefined outcome the expectation that neuromarkers would increase with time postsurgically. Multiple analyses were carried out, with no correction for multiplicity, since the number of tests within each pair-wise comparison was at most four. The relatively low number of significant findings, out of a large number of non-significant findings may therefore have been due to chance and need corroboration in a future study addressing one of the findings as primary outcome. In other words, this should be regarded as a hypothesis-generating study.

Neurologic deficit resulting from time-dependent rSO_2-decrease was previously reported in a study by Slater *et al*. [11], where low rSO_2 lasting >3000 sec was reported to negatively affect neurologic outcome in CPB patients. It is therefore likely that a time-dependent threshold value for desaturation exists. Our results show an association between the change in tau concentration and rSO_2 value lower than 55% when lasting more than ten minutes. However, this might be explained to numerous individual and variable factors (premorbid blood pressure, depth of anaesthesia, type of anaesthetic, localized cerebral vessel pathology, etc.)

It is noteworthy, that time-to-peak was different between NFL (3-5 days) and tau (2 h) suggesting different mechanisms prior to release in systemic blood. NFL was elevated at 3-5 days postoperatively, but was significantly lower at 2 h postoperatively. The 2 h trough might suggest that a systemic effect was at play, for instance, dilution from intravenous fluids or augmented fluid retention. This would dilute protein biomarkers postsurgically, and if so, the tau elevation at 2 h was likely underestimated. Aside from the bi-phasic protein dynamics, this result also suggests that no single external factor, e.g. surgical manipulation, patient positioning are probable confounders. Otherwise, protein markers would be expected to show uniform direction change, whereas we found tau to increase whilst NFL decreased.

By contrast Laflam, *et al* [30] found no difference in neuromarkers S100B, NSE and GFAP, between two groups of shoulder surgery patients, one in BCP, and one in lateral decubitus position (LDP) for general anaesthesia. The rationale was that LDP would incur less decrease in cerebral autoregulation (and rSO2), which was demonstrated, but this did not result in improved post-operative cognitive outcome nor differences in biomarkers. However, S100B and NSE have lower specificity for brain injury than does tau or

NFL, but this study too had limited access to postsurgical blood sample collection, possibly curtailing the ability to relevant test timing, rendering it difficult to find peak values.

The findings from the current investigation cannot stand uncorroborated; the main limitations being that it is a small, noninterventional and uncontrolled study. Hence, we cannot exclude that these changes would not be seen in a control group and we cannot be certain of the cause of the biomarker changes. However, if, for the sake of argument, the changes were caused by a confounding factor, (anaesthesia, position, or surgery) then it seems implausible that one biomarker would increase whilst the other decreased, as was the case. The same accounts for per-operative fluid administration. Based on the present results, we cannot claim that *no* association existed between perioperative changes in candidate biomarkers and regional SO_2. Therefore, repeated, larger, and controlled studies are required. One should remain critical and vigilant to the use of NIRS, and if anything, this investigation has revealed the possibility of further study opportunity with NIRS and biomarkers in concerto. Further, more detailed time resolution, and other biomarkers, would serve well in a longitudinal study with time-resolve to 1 hr.

Controls including sham operations, in addition to different types, need to be conducted to evaluate their effect on biomarkers.

NIRS offers potential as a monitor in the subclinical range of oxygenation, but is still subject to further validation against clinical outcomes. With the relative rarity of preventable serious neurologic outcome, significant patient numbers need to be included to demonstrate clinical benefits of NIRS. Finally, novel neurological biomarkers could help screen patient risk profiles in conjunction with anticipated cerebral circulation compromise, e.g. CPB and beach chair surgery.

In conclusion, this exploratory, observational cohort study of anaesthesia for shoulder surgery in the beach-chair position suggests that serum levels of the biomarkers neurofilament light and tau increased postsurgically with beach chair position and anaesthesia. This finding was partly associated with episodic severe rSO2 desaturation, and postoperative cognitive dysfunction, which however needs corroboration in future studies.

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Author contributions statement

J.R.L., T. K., L.S.R. and H.Z. conceived the experiment, T. K., J.R.L., P.S., K.B. and H.Z. conducted the experiments, J.R.L., H.Z., L.S.R., K.B. and P.S. analysed the results. All authors reviewed the manuscript.

Additional information

Data availability statement: All data is available upon request from the corresponding author.

Acknowledgements

The authors respectfully wish to thank dr Søren Søndergaard for proof reading of the manuscript.

Patient Characteristics n=28	
Age	56.1 (range 21-80)
Gender	16 f; 12 m
BMI	27.3 (range 20.8 - 48.3)
Arterial Hypertension	4 (14.3%)
Diabetes Mellitus, type 2	2 (7.1%)
COPD	1 (3.6%)
Atrial Fibrillation	1 (3.6%)
Mild Aortic Stenosis	1 (3.6%)
Shoulder surgery by operation type:	
Decompression (ASD)	21 (75.0%)
Rotator Cuff Repair	6 (21.4%)
AC joint reconstruction	1 (3.6%)
AC joint resection (in combination with one of the above)	8 (28.6%)

Table 1. ASD=Arthroscopic Subacromial Decompression. AC=Acromioclavicular.

Table 2. Serum neuroprotein concentrations (95%CI). Rank sum (Wilcoxon) paired samples test. Results of investigated predicted associations are given in the lower part of the table.
ns=not significant

Protein (pg/mL)	Baseline (T_0)	2 hours (T_1)	Day 3-5 (T_2)	Significance
NFL	**24.2** (14.4-24.8)	**21.5**[§] (13.7-22.6)	**27.7***(18.1-29.5)	[§] P=.02 vs. T_0 *P=.032 vs. T_0
Tau	**0.77** (0.54–0.94)	**0.98**[†] (0.59-1.21)	**0.81** (0.47-0.86)	[†] *P*=.036 vs. Day3-5
ABeta40	**284.1** (256.3-312.1)	**279.1** (245.0-313.2)	**247.6** (215.2-280.0)	*ns*
ABeta42	**11.8** (10.4-13.2)	**11.0** (9.8-12.3)	**11.1** (9.9-12.4)	*ns*
Other correlation comparisons				
Max. NFL	vs. **NIRS<55%**; *P*=0.019	vs. **NIRS<47%**; *P*=ns	vs. **NIRS<45%**; *P*=ns	Relative NIRS change; not tested
	vs. **z-score 1 wk.**; *P*=ns	vs. **z-score 3 mo.**; *P*=0.018		
Max. Tau	vs. **NIRS<55%**; *P*=ns	vs. **NIRS<47%**; *P*=ns	vs. **NIRS<45%**; *P*=ns	Relative NIRS change; not tested
	vs. **z-score 1 wk.**; *P*=0.012	vs. **z-score 3 mo.**; *P*=ns		
ΔNFL	vs. **NIRS<55%;** *P*=ns	vs. **NIRS<47%;** *P*=ns	vs. **NIRS<45%;** *P*=ns	Relative NIRS change; not tested
	vs. **z-score 1 wk.;** *P*=ns	vs. **z-score 3 mo.;** *P*=ns		
ΔTau	vs. **NIRS<55%**; *P*=0.047	vs. **NIRS<47%;** *P*=ns	vs. **NIRS<45%;** *P*=ns	Relative NIRS change; not tested
	vs. **z-score 1 wk.**; *P*=0.006	vs **z-score 3 mo.**; *P*=ns		

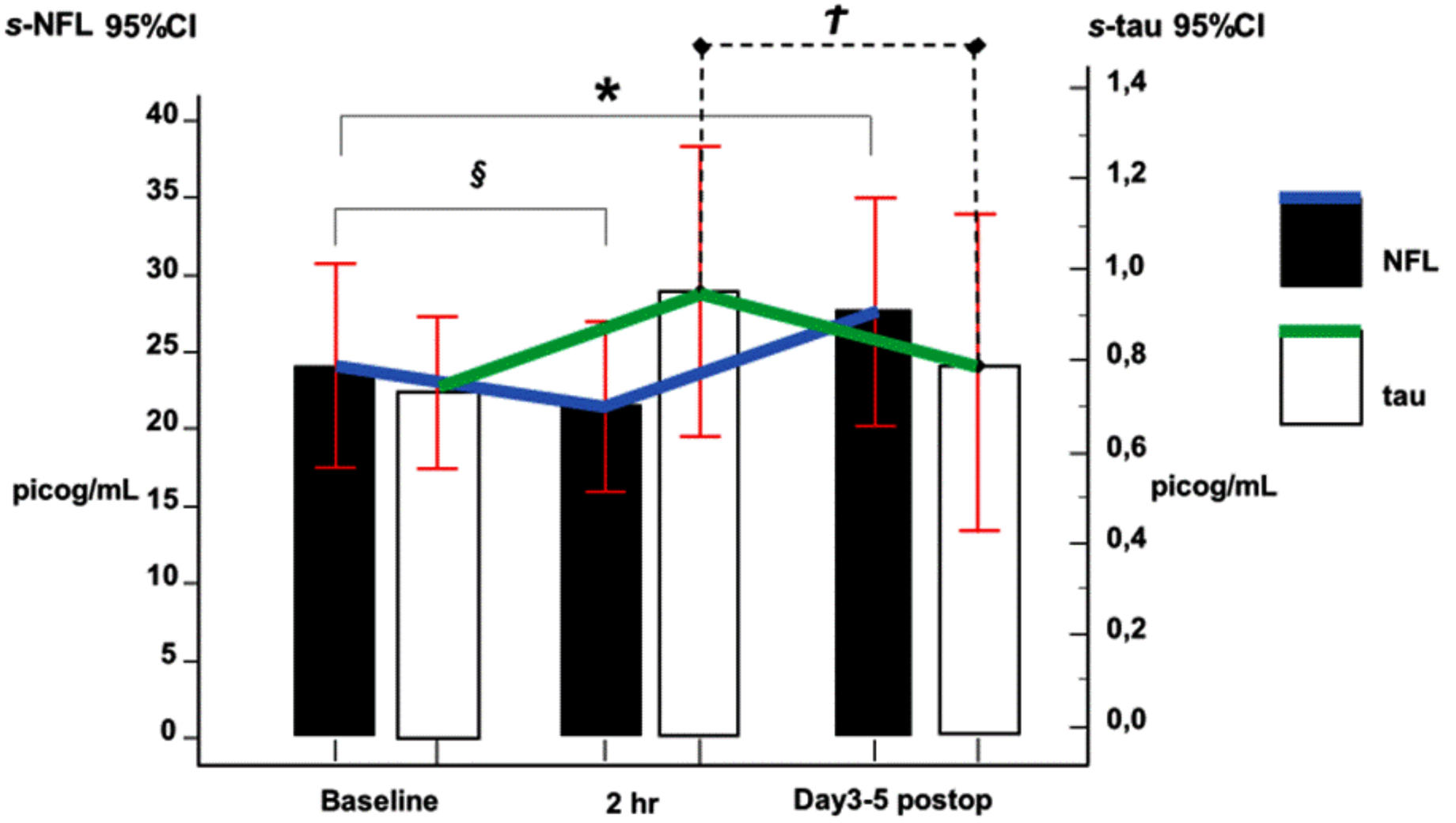


Fig. 1. Serum-neuroprotein [NFL], [tau] concentrations (mean; error bars 95%CI) sequentially (2 h, 3-5 days postop) after TIVA general anaesthesia in the Beach chair position for shoulder surgery in 28 patients. For significance tests ref. Table 1.

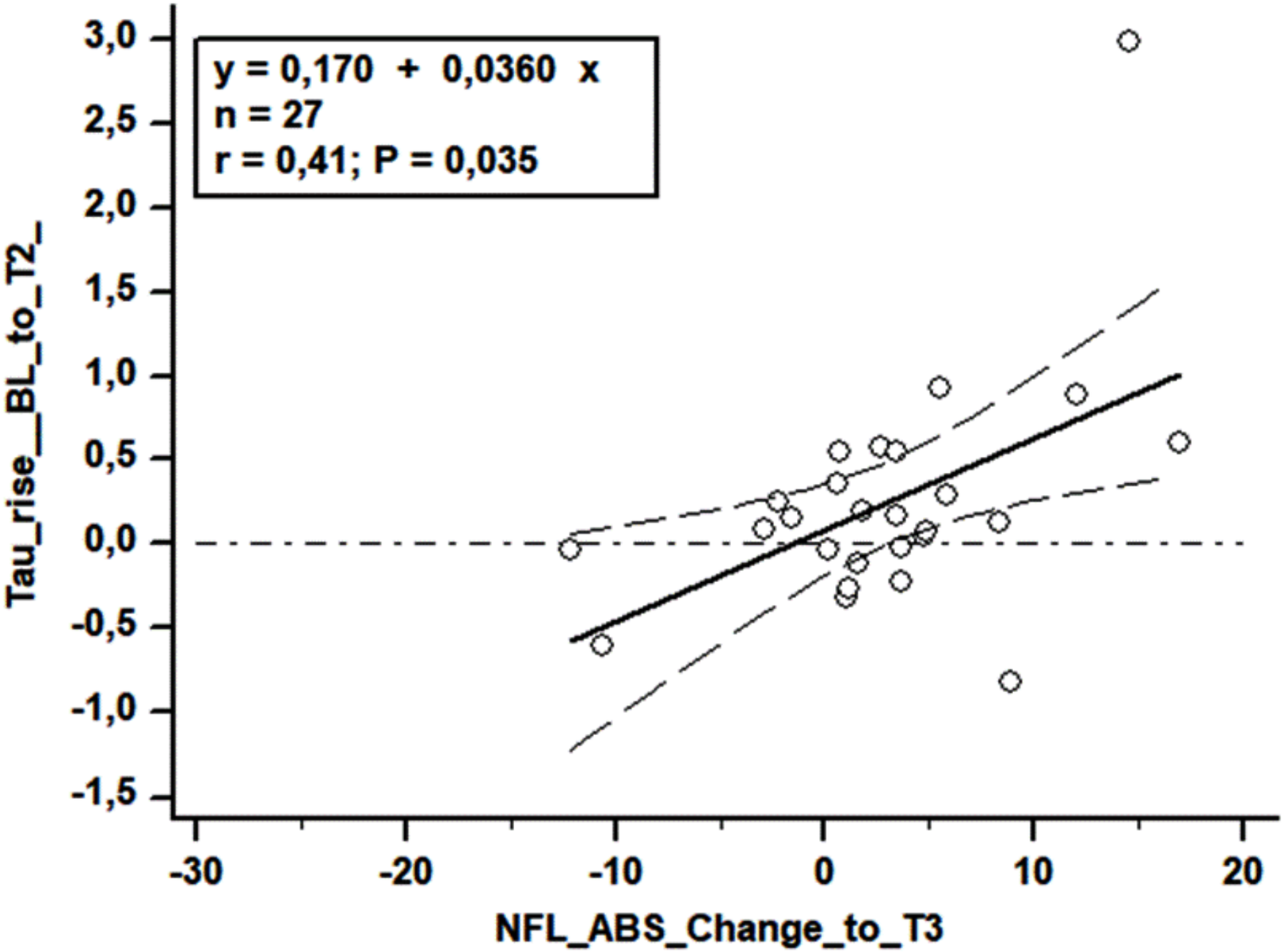


Figure 2. Correlation between change in s-neuroproteins peak level, linear regression (sum of least squares), P=0.035, slope=0.41.

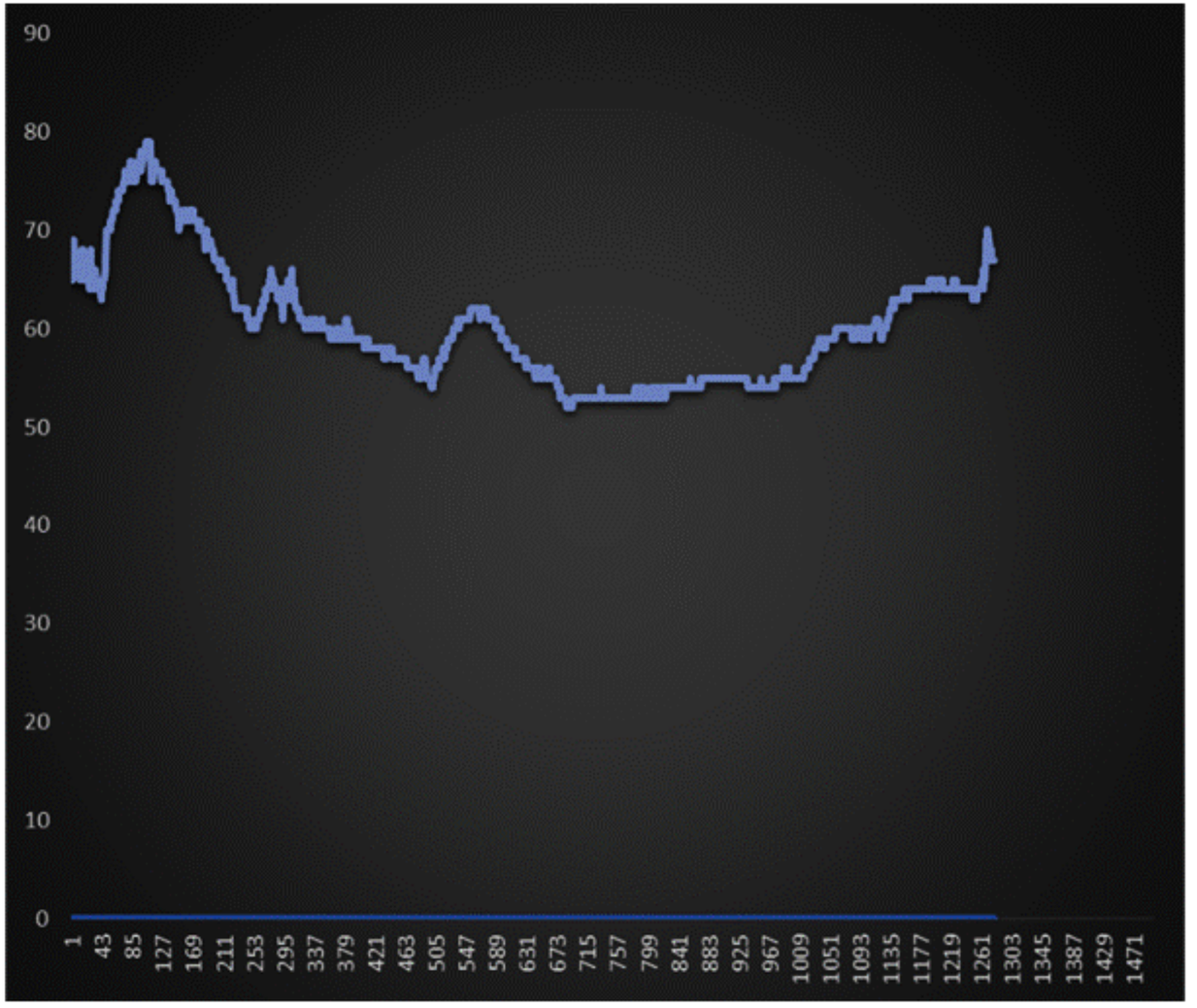


Figure 3. A typical individual cerebral frontal lobe rSO_2-curve readout. Baseline is recorded (far left) prior to anaesthesia induction (67%). Then follows a rise conjoined with preintubation oxygenation (peak at 80%), then return to baseline, subsequently lower during surgery and with lower blood pressure.

Legend: x-axis (seconds), y-axis (rSO2%).

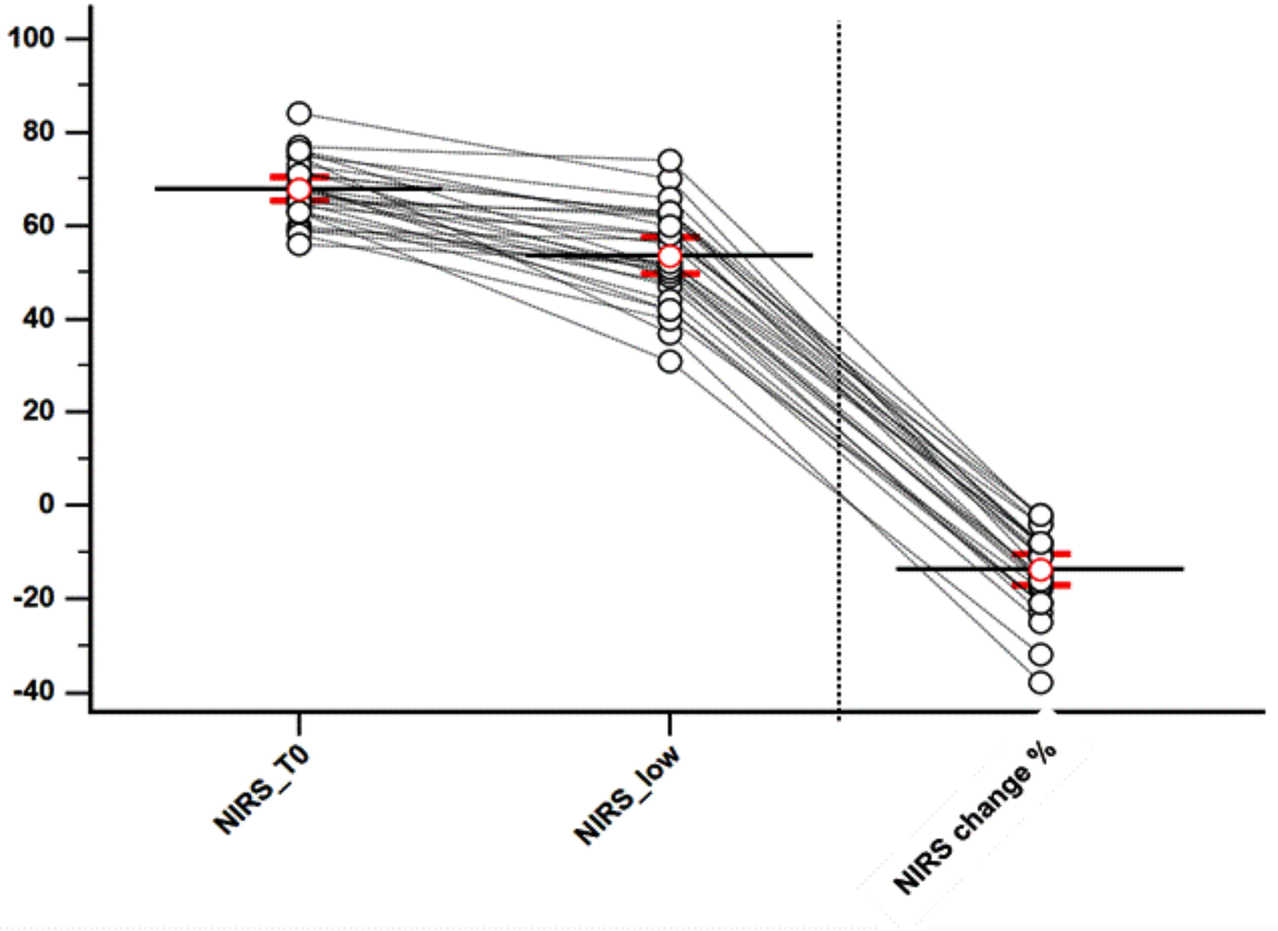
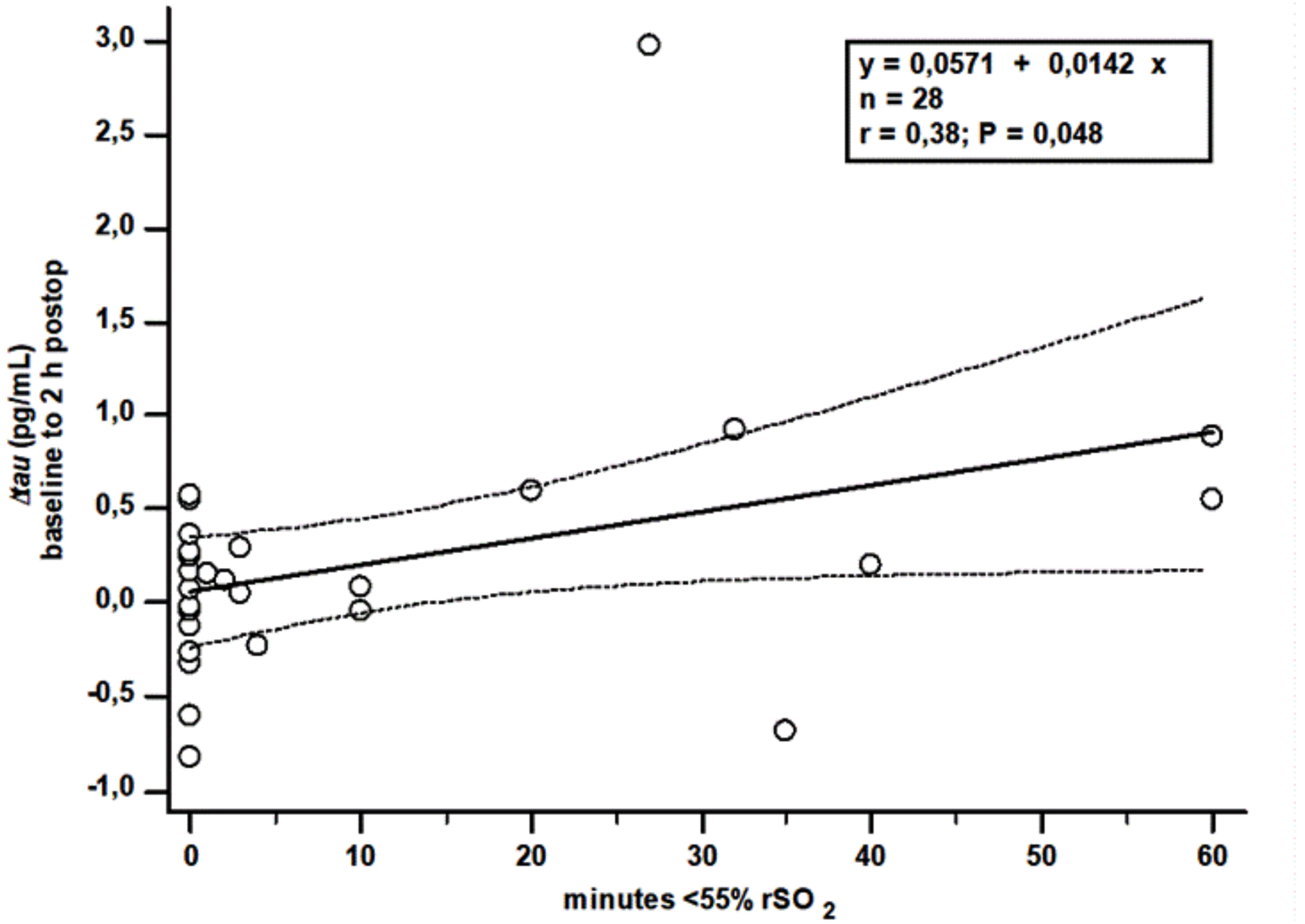


Figure 4. Representation of individual rSO2% (N=28) and summed (mean, 95%CI) at baseline, lowest level, and largest decrease during surgery and anaesthesia. This illustrates that whilst some patients experience negligible decrease, others decline by 40 absolute percentage points from baseline. This was despite standard corrective therapy and maintenance of MAP≥70 mm Hg.

Figure 5. Correlation of s-tau change (Δtau) at 2 h postop to predefined rSO2 <55% (in minutes). Slope=0.38, P=0.048. 95% Confidence Limits. No appreciable change appears until >10 minutes.



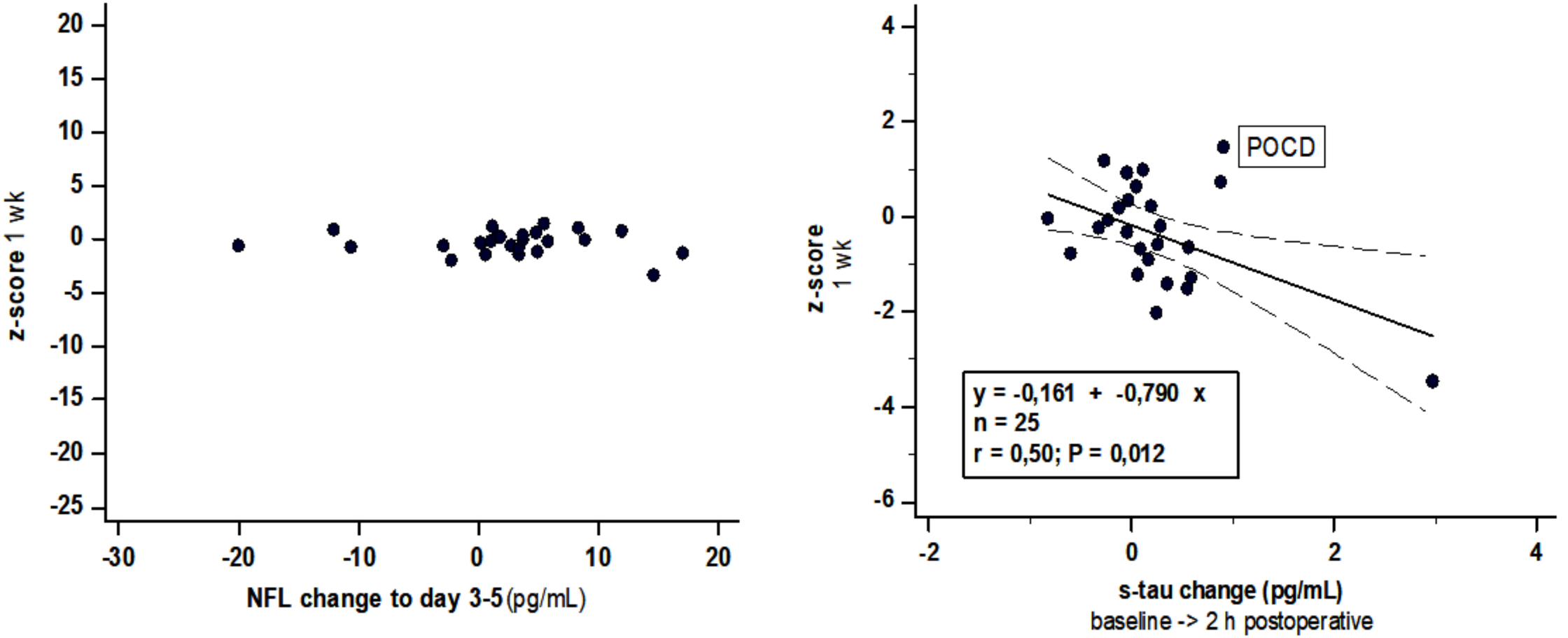


Figure 6. Post-Operative Cognitive Dysfunction: Correlations of POCD z-scores to ΔNFL (P=O.3) and tau change (Δs-tau) (right panel). Sum of least square line: Slope=0.5, P=0.01. (95%CI). Note: The case indicated with POCD had a total tau value of 1.68 pg/mL at 2 h postsurgically (c.f. mean preoperative 0.77).