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Statistical analysis plan for: Dynamic cerebral autoregulation during early orthostatic exercise in patients with severe traumatic brain injury: results from a randomised clinical feasibility trial

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Background

As previously described [1] we conducted a randomised feasibility trial on early orthostatic exercise on a tilt-table in the acute phase of traumatic brain injury at the neurocritical care unit. At three timepoints (baseline, two weeks and four weeks) during the intervention period a head-up tilt test was thus performed to investigate haemodynamic stability.

This document describes the statistical analysis plan assessing haemodynamic variables in the study.

Objective

The objective is to investigate whether dynamic cerebral autoregulation (dCA) is affected in patients with severe traumatic brain injury after four weeks of early orthostatic exercise when initiated as early as possible in the neurocritical care unit. Furthermore, we attempt to elucidate whether any changes in dCA are associated with the occurrence of orthostatic reactions.

Dynamic cerebral autoregulation

Dynamic cerebral autoregulation (dCA) is evaluated by the non-invasive mean flow index (nMxa) in both the supine and upright position, with patients placed in the given position for at least five minutes, unless an orthostatic reaction is triggered in the latter position. nMxa is an index of the correlation between continuous steady-state recordings of non-invasive arterial blood pressure (ABP, meaured by finger-photoplethysmography) and middle cerebral artery blood flow velocity (MCAv, measured by transcranial Doppler) [2, 3].

Measurements were visually inspected for artefacts of ABP and MCAv. The periods with artefacts in just one of the variables resulted in deletion in both. ABP and MCAv are then averaged into blocks of 3 second. The blocks must have at least 50% of valid raw data, otherwise they will be

deleted. Every 60 seconds, i.e. 20 blocks, a Pearson's correlation coefficient between ABP and MCAv are calculated, generating an epoch [4]. Again, at least 50% of blocks must remain, otherwise the epoch will be deleted. Thus, ideally five epochs and five correlation coefficients are created for both supine and standing position. nMxa is then calculated as the average of all five epochs for the given position [2, 5]. A simplified version of the R-script (R 3.6.1, R Core Team, Vienna, Austria) is presented as **Appendix 1**. Patients with poor insonation window or poor-quality transcranial Doppler ultrasound signal are excluded from the analysis.

Lastly, the following indices are calculated:

Cerebrovascular resistance index (CVR) [6]:

$$CVR = MAP/MCAv$$

and Gosling's Pulsatility Index (GPI) [6]:

$$GPI = (\frac{systolic\ MCAv - diastolic\ MCAv}{mean\ MCAv}).$$

Statistical analysis

Patient characteristics at baseline are presented as either mean and standard deviation or median and interquartile range depending on whether data can be assumed to follow a normal distribution. Discrete variables are presented as frequencies, proportions, and percentages. The measured haemodynamic variables are presented per group as mean (SD). The primary analysis will compare the patients' nMxa index at four weeks (end of intervention) using a mixed effects model. The model will adjust for stratification variable (Glasgow Coma Score (GCS) dichotomised as high (7-10) or low (3-6)) and $PaCO_2$ level. Secondly, patients surviving the first four weeks were included in the analysis of changes in nMxa (as a continuous variable) over time using a mixed effects

model. The following co-variates will be used in the model: $PaCO_2$ and stratification (GCS). Thirdly, the presence of orthostatic reactions (hypotension or tachycaardia during HUT) will be applied to the model to test if there is any significant difference in nMxa between patients experiencing orthostatic reactions and those who do not. The model assumptions will be tested using distribution of residuals and logarithmic transformation in case of skewness. Lastly, the covariates included in the model will be tested for interaction, and non-significant interactions are removed from the analysis if not directly used for answering specific questions, such as between group differences at a single time-point. Each of the following variables are analysed using this method: mean ABP, heart rate, MCAv, CVR and GPI.

Lastly, the nMxa was dichotomised as intact dCA (nMxa < 0.3) and impaired dCA (nMxa > 0.3). Fisher's exact test comparing patients with orthostatic hypotension during the HUT with patients experiencing impaired dCA will be performed.

References

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[2] Czosnyka M, Smielewski P, Kirkpatrick P, et al. Monitoring of cerebral autoregulation in head-injured patients. *Stroke* 1996; 27: 1829–1834.

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[4] Riberholt CG, Olsen MH, Skovgaard LT, et al. Reliability of the transcranial Doppler ultrasound-derived mean flow index for assessing dynamic cerebral autoregulation in healthy volunteers. *in review*.

[5] Schmidt B, Czosnyka M, Raabe A, et al. Adaptive noninvasive assessment of intracranial pressure and cerebral autoregulation. *Stroke* 2003; 34: 84–89.

[6] van Beek AH, Claassen JA, Rikkert MG, et al. Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. *J Cereb Blood Flow Metab* 2008; 28: 1071–1085.

Appendix 1 – Simplified R-script

After deletion of artefacts the measurements nMxa is calculated using a similar R-script.

```
setwd(dirname(rstudioapi::getActiveDocumentContext()$path))
df <- read.csv2("recording.txt", sep="\t", header=F)
trigger <- read.csv2("trigger.txt", sep="\t", header=F)

blocksize <- 3; epochsize <- 20; freq <- 1000

df_blocks <- NULL
for(i in c(1:nrow(trigger))){

   temp_df <- df[df$V1 >= trigger[i,1] & df$V1 < trigger[i,2],]

   temp_df$n <- c(1:nrow(temp_df))
   temp_df$block <- ceiling(temp_df$n/(blocksize*freq))
   temp_block <- aggregate(temp_df,list(temp_df$block),mean)[c(2:4,6)]
   temp_block$epoch <- ceiling(temp_block$block/(epochsize))
   temp_block$period <- i

   for(j in c(unique(temp_block$epoch))){
      temp_block$Mxa[temp_block$epoch == j] <-
            cor(temp_block$V2[temp_block$epoch == j],
                temp_block$V3[temp_block$epoch == j])
   }

   df_blocks <- rbind(df_blocks, temp_block)
}

df_periods <- aggregate(df_blocks,list(df_blocks$period),mean)[c(7,8)]
```