STATISTICAL METHODOLOGY AND ANALYSIS

1.1 Analysis sets

The study will be analyzed using the per-protocol set. This analysis set comprises all subjects who underwent treatment with both pressure support systems and did not violate the protocol in a way that might affect the evaluation of the primary study parameter. Drop-outs may occur if the treatment will be interrupted in case of technological failure, emergency situation, unstable cardiovascular or pulmonary conditions, cardiac arrest and cardiopulmonary reanimation. In case of a drop-out, the evaluation of the primary parameter is not meaningful, so that drop-outs will be excluded from the analysis. All treatment interruptions will be documented and summarized.

Violations of the protocol due to a wrong randomization ordering (reverse than randomized) are less likely because measurements are done by one person (Mr. Schnetzinger) who is also the holder of the randomization list.

1.2 Sample size considerations

A sample size calculation has been carried out. Basis for this sample size calculation is preliminary data for the primary endpoint, the high frequency components of heart rate variability (median over one hour measurement per patient, further on denoted as HF). We assume a mean HF of about 49 ms^2 for the conventional mode of mechanical ventilation. An increase of on average 10 ms^2 (to 59 ms^2) for the variable pressure support mechanical ventilation is assumed. For sample size calculation, the standard deviation of the difference was set to 25 ms^2.

When the sample size is 52, a single group t-test with a 0.05 two-sided significance level will have 80% power to detect the assumed effect.

Empirical knowledge of eventual intervention-related drop-out of patients from the study, leads to a sample size of 60 patients. (drop outs due to technological failure, emergency situation, unstable cardiovascular or pulmonary conditions, cardiac arrest and cardiopulmonary reanimation).

1.3 Relevant protocol deviations

Protocol deviations may occur if the treatment will be interrupted in case of technological failure, emergency situation, unstable cardiovascular or pulmonary conditions, cardiac arrest and cardiopulmonary reanimation. In case of a drop-out, the evaluation of the primary parameter is not meaningful, so that drop-outs will be excluded from the statistical analysis.

1.4 Statistical analysis plan

see 11.6

1.5 Missing, unused and spurious data

Missing, unused or spurious data due technological failure, emergency situation, unstable cardiovascular or pulmonary conditions, cardiac arrest and cardiopulmonary reanimation will be reported and presented. Records with missing data will be excluded from the analysis.

1.6 Endpoints analysis

1.6.1 Primary endpoint analysis

The median of the high frequency components (HF) measured over one hour per patient will be described descriptively separately for the two pressure support mechanical ventilation groups using means, standard deviations as well as medians and quantiles. Graphical illustration will be performed using boxplots.

To compare the mean HF between conventional and variable pressure support mechanical ventilation, first a paired t-test will be performed.

Furthermore, an ANOVA for repeated measurements, accounting for group (conventional vs. variable), randomization order, the interaction between group and randomization order as well as other influence factors (as gender and age) will be performed.

The significance level for the primary analysis is set to 0.05.

1.6.2 Secondary endpoint analysis

Similar to the main outcome parameters the median of the standard deviation of normal to normal (SDNN) and the median of high-frequency-low-frequency-ratios (HF-LF-ratio) over one hour measurements will be described descriptively with boxplots as well as means, standard deviations, medians and quantiles.

Furthermore, mean SDNN and HF-LF-ratio will be compared between treatment groups using paired t-tests. In addition, an ANOVA for repeated measurements, accounting for group, randomization order, the interaction between group and randomization order as well as other influence factors (as gender and age) will be performed.

The significance level for the secondary analyses is set to 0.05.

1.6.3 Safety and tolerability endpoints

The occurrence of adverse events will be described descriptively by frequencies and percentages.

1.6.4 Exploratory analyses

All exploratory parameters, which are obtained from arterial blood gas analysis (systolic and diastolic arterial blood pressure, arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide) will be described with descriptive statistics (boxplots, means, standard deviations, medians and quartiles) separately for the two groups.

1.7 Interim analysis

No interim analysis is planned.

Criteria for the termination of the clinical investigation:

Not applicable as no interim analysis planned.

1.8 Software program(s)

Statistical evaluation will be performed using SPSS and R.