**IROI respiratory substudy – statistical plan**

Adrian Regli, Annika Reintam-Blaser, Bart De Keulenaer, Joel Starkopf, Edward Kimball, Vernon Van Heerden, Wendy Davis

**Background**

Intra-abdominal hypertension (IAH) is associated with increased atelectasis formation, reduced chest wall compliance and lung volumes. Some data indicate that IAH is more prevalent in patients with respiratory failure (1, 2). In addition, patients with respiratory failure (PaO2/FiO2 ratio < 300 mmHg) are more likely to have IAH (2).

Furthermore, data from animal experiment and physiological experiments in humans indicate that lung mechanics per se and the effect of PEEP on lung mechanics are different in the presence of IAH (3–7).

It is therefore possible that patients with respiratory failure can be characterised by the presence or absence of IAH and that these two patient subgroups might differ in terms of outcome and treatment required.

To our knowledge there are no prospective observational studies examining the relationship between respiratory failure and IAH.

**Aims**

The primary aim is to assess whether IAH (on admission or developed during ICU stay) is an independent risk factor in patients with respiratory failure (receiving invasive ventilation and have a PaO2/FiO2 ratio < 300 mmHg) for 90-day mortality.

Secondary aims include:

To assess whether IAH (on admission or developed during ICU stay) is an independent risk factor in patients with respiratory failure (receiving invasive ventilation and have a PaO2/FiO2 ratio < 300 mmHg) for the following outcomes: 28-day mortality, ICU length of stay, hospital length of stay, and time spent on the ventilator.

To assess the prevalence (day of admission) and incidence (after admission and occurring at any time during their ICU stay) of IAH and compare the outcomes of the following four patient subgroups:

1. Patients who never developed respiratory failure or IAH
2. Patients who never developed respiratory failure but have or developed IAH
3. Patients with respiratory failure (on admission or developed during ICU stay) but never developed IAH
4. Patients with respiratory failure (on admission or developed during ICU stay) and IAH (on admission or developed during ICU stay)

To determine the ventilation characteristics of the subgroups c) and d) such as: PEEP and FiO2 used, airway pressures, driving pressures, tidal volumes.

To assess the risk factors for the development of respiratory failure in patients with and without IAH on the day of admission, who did not have respiratory failure on admission.

To assess whether a time relation exists between the development of IAH and the subsequent development of respiratory failure.

**Hypotheses**

The primary hypothesis is that IAH (on admission or developed during ICU stay) is an independent risk factor for 90 day mortality in patients with respiratory failure (receiving invasive ventilation and having a PaO2/FiO2 ratio < 300 mmHg).

The secondary hypotheses are:

1. That IAH is an independent risk factor for 28-day mortality, ICU length of stay, hospital length of stay, and time spent on the ventilator in patients with respiratory failure.
2. That patients who never develop respiratory failure or IAH have better outcomes than patients who develop respiratory failure or IAH.
3. That patients who develop both IAH and respiratory failure have worse outcomes than patients who develop IAH or respiratory failure alone.
4. That patients who develop respiratory failure are ventilated differently depending on the presence or absence of IAH.
5. Patients that develop IAH and respiratory failure develop IAH before they develop respiratory failure.
6. That, in patients without respiratory failure on admission, the risk factors for developing respiratory failure differ in patients with and without IAH (on admission or developed during ICU admission).

**Methods**

The IROI study is an international multicentre prospective observational cohort study aiming to describe the incidence, risk factors and outcome of IAH in critically ill patients (8).

In a pre-planned manner, we prospectively observed additional parameters as part of the IROI study to investigate whether IAH leads to respiratory failure and related adverse outcome in critically ill patients with IAH.

For simplicity, respiratory failure will be defined as patients receiving mechanical ventilation and have a P/F ratio < 300 mmHg. Respiratory failure will be graded into mild (P/F 200 to 300 mmHg), moderate (P/F 100 to < 200 mmHg), and severe <100 mmHg). IAH is defined as sustained IAP ≥ 12 mmHg (9). IAH is graded from I to IV based on IAP of 12 to 15, 16 to 20, 21 to 25 and > 25 respectively (9).

Daily median IAP as well as daily lowest P/F ratio, highest positive end-expiratory and peak and plateau airway pressure in H2O, highest expiratory tidal volume in mL, highest respiratory rate were prospectively collected.

Outcome variables will include intensive care unit (ICU) mortality, length of time spent on a mechanical ventilator, length of stay in ICU, length of stay in hospital, 28 day and 90 day mortality.

**Statistics**

The computer package IBM SPSS Statistics will be used for statistical analysis. Data will be presented as proportions, mean±SD, geometric mean (SD range), or, in the case of variables which do not conform to a normal or log-normal distribution, median and interquartile range. For independent samples, two-way comparisons for proportions will be by Fisher’s exact test, for normally distributed variables by Student’s t-test, and for non-normally distributed variables by Mann-Whitney U-test. A two-tailed significance level of P<0.05 will be used.

The prevalence of IAH on admission to ICU and the incidence of the development of IAH during the first 7 days following admission will be calculated. Four sub-groups will be identified based on the presence on admission to ICU or development in the first 7 days following admission to ICU of IAH and/or of respiratory failure.

For the first aim, time-dependent Cox regression will be used to identify predictors of all-cause death in patients with respiratory failure within 90 days of admission to the ICU. The presence of IAH on admission or within the first 7 days following admission will be a time-dependent variable. Follow-up will be censored at death or 90 days after admission, whichever comes first. The same method will be used to identify predictors of 28-day mortality in patients with respiratory failure, a secondary aim, with follow-up censored at death or 28 days after admission, whichever comes first. In patients with respiratory failure,

multiple linear regression will be used to assess whether the presence of IAH on admission or within the first 7 days following admission is independently associated with the following secondary endpoints: ICU length of stay, hospital length of stay, and time spent on the ventilator.

Using the same statistical methods, these five outcomes will be compared by IAH/respiratory failure sub-group to determine whether the presence of both conditions is more detrimental than one alone or none, independent of other known explanatory or confounding variables.

In ICU patients without respiratory failure on admission, time-dependent Cox regression will be used to identify risk factors for the development of respiratory failure, with the presence of IAH on admission or within the first 7 days following admission a time-dependent variable.

Assoc/Prof Wendy Davis from the University of Western Australia will provide assistance in statistical analysis.

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