DISCUSSION OF HEMORRHAGE MODELS

Hemorrhage models allow researchers to simulate the physiologic response to hypovolemic shock. In addition, researchers can also simulate resuscitation, the usual clinical response to shock physiology. Obviously, as shock progresses, mortality increases. Different hemorrhage models offer different advantages. To select the correct model for a study, researchers must weigh the advantages and disadvantages of different models.

Perhaps the most commonly used large animal model in the study of anesthetics is the isobaric hemorrhage model that is often implemented in rodents and swine. As suggested by the name, the isobaric hemorrhage model produces a reproducible, controlled state of shock by progressively bleeding the animals to maintain a constant hypotensive target (typically 40 mmHg). 1-5 After a stable period following instrumentation, animals are bled via a femoral arterial catheter by a roller pump that is automatically guided by the invasive blood pressure readings. Blood is removed at a rate appropriate to achieve a linear decrease in the mean arterial blood pressure to a targeted pressure over a set time period, usually 20 minutes. Once the target MAP is achieved, blood is removed or reinfused via the roller pump to maintain the MAP target.

The isobaric hemorrhage model exhibits two phases. The first phase, called the compensatory phase, is defined as the time during which blood must be continuously removed in order to maintain the targeted level of hypotension; this phase typically lasts approximately one hour. The second phase, called the de-compensatory phase, begins when the previously shed blood must be reinfused in order to maintain the low MAP. Control animals have the same instrumentation, followed by a sham-hemorrhage and identical waiting period to ensure equivalent times under anesthesia and mechanical ventilation. Shock investigators have pointed out the obvious correlation between the length of the compensatory phase in animal models and the “golden hour” of trauma care, a concept that is well entrenched clinical dogma, though somewhat controversial.6 By having the correct monitors in place, researchers can distinguish between different phases of shock (e.g. compensated vs. uncompensated).

To be confident that the clinical pharmacology studies are done at an equivalent degree of shock, drug infusion typically begins at the onset of the de-compensatory phase, an endpoint that is clearly identifiable. The study drug is typically administered intravenously at a constant rate. Arterial blood samples are collected at scheduled intervals for subsequent measurement of the drug concentration. For anesthetics, PD effect is typically measured using the processed electroencephalograph as the surrogate outcome signal.

The plasma drug concentration and effect signal data are then analyzed to build a combined PK-PD model that characterizes the influence of bleeding on the disposition and effects of the study drug. Clinical inference about rational drug selection and administration is then drawn from simulations applying these pharmacologic models.

Another common hemorrhage protocol used in studies such as these is the isovolemic hemorrhage model, often implemented in rodent models.7-15 In this paradigm, hypovolemia is induced by removing a set percentage of the estimated total blood volume (e.g. 30% of an estimated 60mL/kg total blood volume in rats). The model is considered isovolemic in that a set volume of blood is removed and then no further hemorrhage occurs. The target shed-blood volume is achieved by removal in several increments over a short period (e.g. 6 bleeds over 30 minutes). Control animals have an equal volume removed and immediately reinfused to prevent development of shock.

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