

# Protocols for lung protective ventilation

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Protocols have a well-established role in clinical research and are increasingly being used to direct routine clinical care. In this article, we review the differing goals of research and clinical protocols and outline the similar process for their development. We use the mechanical ventilation protocol of the ARDS Network trial comparing small with traditional tidal volumes as an example. As a starting point for debate, we also suggest guiding principles and specific

components of a protocol for high-frequency oscillatory ventilation. (Crit Care Med 2005; 33[Suppl.]:S223–S227)

**KEY WORDS:** process of care; protocols; decision support; clinical research; clinical trials; mechanical ventilation; high-frequency oscillatory ventilation; acute respiratory distress syndrome; ventilator-induced lung injury; lung-protective ventilation

A spectrum of decision support tools is available to assist in the management of complex patients. Protocols, which lie near one end of the spectrum, are sets of explicit, algorithmic rules, which direct clinical management or research. They must be distinguished from guidelines, a set of principles, goals, or suggestions that may also direct clinical or research decisions. In general, guidelines are more general, flexible, and tolerant of latitude among clinicians. They lie closer to the other pole of the decision support tools spectrum. Protocols, although not necessarily inviolate, are more specific in their instructions. The distinction is somewhat arbitrary, but a useful working definition is that a protocol is a set of rules that will lead varied practitioners, faced with the identical clinical situation, to reach the identical decision.

Protocols have long been recognized as essential to the performance of prospective clinical research and are being used increasingly for clinical care. We believe they are particularly valuable to guide the use of unfamiliar or complex interventions such as high-frequency oscillatory ventilation (HFOV). However, we will first distinguish between their use for clinical research and clinical practice, because these distinctions have implica-

tions for the design, implementation, and effects of protocols.

## Research Protocols

In clinical research, the most apparent need for a protocol is to direct the application of the intervention under study, for example, in a randomized trial. Analogous to specifying the quantity, frequency, and administration route of an investigational drug, the application of a new intervention must be well-defined to assure that the study group receives an appropriate “dose.” For example, in the ARDS Network (1) trial comparing small with traditional tidal volumes in acute lung injury/acute respiratory distress syndrome (ALI/ARDS), there were explicit instructions to determine the size of the tidal volumes in the lower tidal volume arm.

A somewhat more controversial application of protocols in clinical research is their use to direct the management of the control or comparison arm in regard to the intervention under study (2). One approach is to allow the comparison arm to receive “usual care,” care delivered by the judgment (or whim) of the treating physician. The alternative is to provide an explicit protocol, which limits the clinicians’ range of choices while embodying a process of care that many practitioners would have chosen were they providing usual care to similar patients. Each trial design may be appropriate for different research questions. However, “usual care” in critical care is often highly variable, and the determinants of clinicians’ varied choices are obscure. In unblinded trials, patient management decisions may

also be altered by the very existence of the study (the Hawthorne effect). Therefore, use of usual care as a control arm will tend to reduce a treatment effect, perhaps rendering it immeasurable. If effects are detected, the specific determinants of the outcome are more difficult to define. A recent randomized trial of prone vs. supine positioning for hypoxemic respiratory failure exemplifies this problem (3). This study tested the effect on mortality of an intervention, prone positioning, that may protect the lung from ventilator-induced injury. However, there was no systematic control of the strategy of mechanical ventilation in either arm, and prone positioning was allowed in the control arm if clinicians felt it was indicated (despite the absence of data on its efficacy). This resulted in a 21% crossover rate, and there was no difference in mortality between the study groups.

A final role for protocols in clinical research is to reduce confounding by other aspects of care that may affect outcomes but are not themselves the intervention under study. Given the complexity of care for the critically ill, this may appear unobtainable. Some trials have gone to great lengths to control aspects of clinical care (4). However, the most important issues to control by protocol would be those likely to both affect outcomes and to vary between study arms. Examples in studies of mechanical ventilation are the approach to weaning (1) or the use of sedatives and paralytics (5). In the ARDS Network tidal volume study, ventilator-free days was an important outcome variable. Because it was impossible to blind the clinicians to study

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group assignment, there was a potential for systematic differences in the approach to weaning between study groups. Therefore, weaning in both arms was controlled by the same protocol. The complex environment of the intensive care unit creates a very “noisy” field in which to distinguish a treatment effect. The use of protocols to manage ancillary aspects of care helps to decrease the noise attributable to unnecessary practice variation and potentially reveal the signal.

## Clinical Care Protocols

The use of protocols to guide routine clinical care outside of the research setting is a more recent development in critical care with a distinct set of goals and requirements. At least four goals can be served. First, the protocols reduce the degree of variability inherent in usual care. To the extent that evidence or expert opinion supports one management style over others, patient outcomes may improve by increasing compliance with the evidence.

A second, but related, goal is the rapid integration of new information into clinical practice. Several studies have shown that clinicians are slow to change their practice after the publication of new findings (6, 7). Several explanations for this inertia have been suggested (8). However, protocols can speed this process by making the preferred approach the default approach and requiring more effort or thought to deviate to other strategies.

A third goal is to redistribute workload. A well-designed clinical protocol can clarify decision-making, allowing poorly understood judgment by physicians to be replaced by more deterministic decisions that can be made by nurses or therapists. An example of this is the various protocols for ventilator weaning by nursing and respiratory care staff, which have been shown to decrease time on mechanical ventilation in several settings (9–11). To the extent that physician time is more expensive, this redistribution of workload can result in cost savings even if it has no effect on clinical outcomes. However, involving additional skilled personnel in a process of care traditionally reserved for physicians can often both reduce costs and improve outcomes. Relatively simple protocols for scheduled weaning by nurses and therapists have often hastened extubation compared with the complex physiological measures and judgments of physicians.

This suggests that the *regularity* of steps enforced by a protocol as executed by nurses or therapists trumps the rarified individual decisions made sporadically by busy physicians.

Finally, protocols can facilitate medical education. It may seem counterintuitive that a tool that reduces the need to think carefully and individually about each patient can be a teaching tool. However, the process of protocol development (discussed subsequently) includes a thorough review of relevant data and expert opinion, consideration of current local practice and patient needs. It clarifies, as well as codifies, the state-of-the-art on a specific patient management question. The protocol provides a template for explaining *why* it represents the preferred mode of therapy, much like the periodic table of the elements can be used as either a simple reference chart or a rich distillate of chemistry and physics.

Clinical protocols have also been criticized. First, there is the potential loss of the individualization of care, or subversion of the art of medicine (12). This criticism, in part, assumes that variations in usual care result from thoughtful titration rather than individual prejudice, routine, style, or inattention. The criticism is also more validly leveled at a poorly designed protocol that does not anticipate the range of circumstances in which it will be applied or allow for individual titration within a goal range. Second, protocols may be criticized if they are applied in populations beyond which they have been tested. This, too, is a failure of protocol design rather than of protocols per se.

Despite these potential shortcomings, clinical protocols in critical care have been shown to improve medication use (13), weaning (9), glucose control and associated mortality (14), and nutrition support (15). Their use has been encouraged by published practice guidelines (16). As results from studies using research protocols continue to inform clinicians about the best management decisions, clinical protocols will remain practical tools to implement those decisions at the bedside.

## How to Construct a Protocol

Research protocols are often implemented by focused, motivated research personnel or by clinicians closely supervised by researchers. This allows research protocols to be detailed and relatively

complex while still assuring compliance. In contrast, clinical protocols are applied by busy doctors, nurses, and therapists who are juggling numerous tasks. Improved patient outcomes are a high priority, but the benefits of protocol adherence for individual patients are not directly visible. Protocols may also be perceived as constraints to clinician choice or judgment. Therefore, clinicians may not be as committed as researchers to adherence with a protocol. Clinical protocols will be followed in proportion to their simplicity, the consistency of their decision instructions with reasoned clinical judgment, the thoroughness and enthusiasm with which staff are trained, and the payback they provide in reduced workload or obvious improved outcomes. Despite differences in their final structure, the processes of protocol development for research or clinical care are similar. In either case, the effort needed to design and implement a protocol successfully is also frequently underestimated.

Protocol development, like critical care, is a team process. Protocols imposed by an individual are doomed to failure. The team must include broad medical knowledge and representation from the disciplines that will be implementing the protocol. Broad representation will quickly uncover flaws that would impede implementation and will build a sense of ownership and commitment from participants. The process should begin by identifying the goals of the protocol and the population in which it will be used. This will be assisted by a review of available data, including published similar protocols, local practices and opinions, and any available guidelines.

The review will assemble a variety of practices, preferences, and protocols supported by evidence of variable quality. The next step is winnowing these options down to a consensus. Formal methodologies for consensus-building have been developed such as the Delphi technique or the Nominal Group Process. These are seldom used in protocol development, which typically relies on informal “brainstorming.” Informal methods, however, risk domination by those with the most strongly held or passionately expressed opinions. For that reason, it is important that candidate protocols be reviewed by practitioners outside of the development committee early in their genesis. This will ensure that they do not stray so far

from accepted practice that they are unlikely to be followed.

After an approach is agreed on, the general strategy must be distilled into a set of rules or a decision tree. This is a critical step, which requires unambiguous decision rules that anticipate a broad range of possible contingencies. Decision rules will be applied most consistently when based on objective and quantifiable data such as a respiratory rate or PaO<sub>2</sub> rather than subjective factors such as whether a patient appears dyspneic. Compromises must be made between the specificity and complexity of the protocol; as protocols attempt to control more details, they become exponentially more complicated and adherence suffers.

Once a protocol has been committed to paper, it should be submitted to an iterative process of pilot testing and revision. This will reveal aspects that are too restrictive, too lax, too complicated, or simply illogical. When a practical protocol has been built, a more extended pilot should be undertaken. This will uncover flaws by exposure to a wider range of patients and staff. For example, we performed a trial of small vs. traditional tidal volumes in ARDS in four hospitals in Baltimore (17). The experience from that trial assisted protocol development for the much larger multicenter trial undertaken by the ARDS Network (1). The pilot is also the opportunity to develop and test the educational program that will be needed for wide implementation and to refine data reporting forms that will be used to track adherence or efficacy.

Before implementation, staff must be educated. The details of this process will vary with the specific aspects of the protocol. It will involve personnel from various disciplines with different skills and levels of insight and motivation who must all be motivated to alter their practice. When the protocol is implemented, plans must be in place to monitor their compliance and provide feedback and encouragement. Finally, because compliance with the protocol is not the goal in itself, it is useful to collect data documenting the impact of the protocol on patient outcomes, costs, or other goals. This will serve to motivate the clinicians and justify the investment in protocol development.

This process is laborious and not invariably successful. Ely et al. (18) documented the steps they used to extend a simple weaning protocol throughout their hospital after demonstrating its ef-

ficacy in the medical intensive care unit. The process took a full year. Even in their experienced hands, compliance was <65% and quickly fell when ongoing education and reinforcement was stopped. A weaning protocol for pediatric patients, which was the subject of a recent multicenter trial (19), took an estimated 250 man-hours to develop (20).

### Protocols for High-Frequency Oscillatory Ventilation

HFOV for adult ALI/ARDS is both a complex and unfamiliar technology for which research protocols are essential. Guidelines for the use of HFOV in adults are widely available and discussed elsewhere in this supplement. However, outcome benefits of HFOV compared with the best lung-protective mechanical ventilation strategy have yet to be demonstrated. Given the high acquisition costs of HFO ventilators, suitable for only a minority of ventilated patients, outcome advantages must be demonstrated to justify the widespread use of this technology. This will require rigorous comparison between well-defined conventional and HFOV strategies in large clinical trials. These, in turn, will require that both strategies be directed by protocols. Until the results of such trials are available, clinical protocols will also be useful to direct the use of this unfamiliar technology in a way that maximizes its safety and efficacy.

The >2 decades of experience with HFOV in neonatology provides some instructive lessons for adult practitioners. The earliest large randomized trial of HFOV in neonates failed to recognize the importance of lung recruitment to minimize ventilator-associated lung injury. HFOV was applied using relatively low mean airway pressures (mPaw) of only 8–10 cm H<sub>2</sub>O. In this study, HFOV did not reduce the incidence of chronic lung disease or mortality, but a higher incidence of some complications occurred in the HFOV group (21). This experience reminds us that protocols not based on sound pathophysiological insight may harm patients and doom a promising technology.

More recent trials comparing HFOV with conventional ventilation in neonates have used protocols that favored higher mPaw. Nevertheless, two recent large, multicenter trials enrolling similar patients came to differing conclusions. In one, HFOV reduced the incidence of

chronic lung disease at full gestational age (22). The other found no benefit of HFOV (23). These discordant conclusions suggest that the treatment effect is modest, and that small variations between protocols for HFOV or conventional ventilation may be sufficient to alter the outcome of the trial.

It is difficult to trace the ontogeny of the ventilator-setting guidelines for HFOV in adults. We believe they have evolved from settings used in pediatric and trial and error during early experience in adults. Moreover, they were built largely on the immediate feedback from physiological outcomes such as blood gas improvement (positive feedback) or hemodynamic compromise (negative feedback). This resulted in an approach that yields acceptable gas exchange and hemodynamics in most patients. There is extensive evidence, however, that gas exchange is not an accurate surrogate for survival in ALI/ARDS. Interventions such as inhaled nitric oxide (24) or higher levels of PEEP (25) improved oxygenation without improving survival. The use of tidal volumes of 6 mL/kg predicted body weight had deleterious effects on gas exchange but improved survival (1). Thus, with survival as the goal, we have little evidence that current guidelines for HFOV in adults are optimal.

We propose that the protocols for HFOV in adults be guided by the following principles, each of which is either directly supported by animal and human data or extrapolated from such data:

1. Smaller tidal volumes are less injurious than larger tidal volumes.
2. For any given steady-state level of arterial CO<sub>2</sub>, the benefits of smaller tidal volumes are not negated by associated higher respiratory rates.
3. Relatively high airway pressures are less injurious if the lungs are distended at a nearly static volume than if exposed to the same pressure and volume only at the peak of each conventional tidal breath. These three points are the foundation for the use of HFOV as a form of lung protective ventilation.
4. High pleural pressures accompanying effective lung recruitment will compromise venous return, and high transpulmonary pressure may increase right ventricular afterload. The resulting need for volume resuscitation may negate beneficial effects of recruitment on lung injury.

## HFOV Quick Guide

5. Neuromuscular blockade or deep sedation may prolong the duration of mechanical ventilation. Because these medications are often required during HFOV, the duration of HFOV use should be minimized.
6. Lung protective ventilation will be most beneficial when applied early in the course of ALI/ARDS, before ventilator-induced injury is widespread.

From these principles, we derive the following more specific recommendations for protocol design (each of which we offer as a starting point for debate):

**Patient Selection.** HFOV has been shown to improve gas exchange, but its effect on patient outcomes relative to lung-protective conventional ventilation is unknown. Presumptive beneficial effects on lung injury are accompanied by the potentially deleterious effects on hemodynamics, sedation requirements, and impaired ability to perform a physical examination. For these reasons, we believe the clinical application of HFOV should be limited to patients who are failing conventional ventilation. Such failure should be documented by inability to maintain thresholds of oxygenation or ventilation on lung-protective conventional ventilation. For a research protocol, on the other hand, lung-protective benefits of HFOV will be most demonstrable if it is begun early in the course, within 24–48 hrs of meeting criteria for ARDS. Limiting such a study to patients who have failed conventional ventilation will make it ethically difficult to justify randomization, because physicians may insist on its use as rescue therapy. Moreover, such a trial may select a population of patients too late to benefit from HFOV.

**pH Goal.** Modest degrees of hypercarbic acidosis (pH >7.25) should be acceptable, because a goal of normal pH will require either larger or more frequent breaths.

**Frequency.** Given the influence of tidal volume on survival in ARDS, it would be very useful to know the tidal volume during HFOV to titrate settings to individual patient mechanics. Lacking this information, we should choose settings that minimize tidal volume. Rather than begin HFOV at 5 Hz and only reduce frequency if necessary to correct hypercarbia, we recommend that HFOV be used at the *highest* tolerated frequency together with maximal oscillation amplitude (delta P). Our rationale for this is that, for a given PaCO<sub>2</sub>, tidal volume will

### Management of Ventilation

**Overall goal:** Maintain pH in the target range at the *minimum tidal volume*. This is achieved by favoring higher frequencies over lower ΔP. This goal is also promoted by accepting mild respiratory acidosis rather than attempting to normalize pH.

**Monitor:** Obtain ABG at least 30 minutes after each change in settings. Check ABG BID in patient on stable settings.  
**Target pH:** 7.25–7.35  
**Target f:** 12 Hz

**Initial settings:**

- $f = 5$  Hz
- $\Delta P = \text{PaCO}_2$  on conventional ventilator + 20

#### Subsequent adjustments:

- pH in target range**
- Increase  $f$  and increase ΔP as follows:
    - a) Increase  $f$  in increments of 1–2 Hz to max. of 12 Hz
    - b) If pH falls below acceptable range at any  $f$ , increase ΔP in increments of 5 cmH<sub>2</sub>O to max. of 90 cmH<sub>2</sub>O

#### pH too high (Correct metabolic alkalosis, if indicated)

- Increase  $f$  in increments of 1–2 Hz to max. of 12 Hz, then
- Decrease ΔP in 5 cmH<sub>2</sub>O increments to minimum of 20.

#### pH too low (Correct metabolic acidosis, if indicated)

(Consider possible pneumothorax, partial endotracheal tube occlusion, decruitment)

- a) Increase ΔP in increments of 5 cmH<sub>2</sub>O until 90 cmH<sub>2</sub>O, then
- b) Add 5 cmH<sub>2</sub>O cuff leak<sup>1</sup>, then
- c) Decrease  $f$  in 1 Hz increments to minimum of 3 Hz.

<sup>1</sup> A 5 cmH<sub>2</sub>O cuff leak is produced by deflating the endotracheal tube cuff until mPaw falls by 5 cmH<sub>2</sub>O, then increasing bias flow rate to restore MAP to initial value.

### Management of Oxygenation

**Overall goal:** Increase lung recruitment while avoiding overdistension; balance risks of overdistension versus oxygen toxicity. Mean airway pressure (mPaw) is used to recruit lung. Increased mPaw is favored over increased FiO<sub>2</sub> unless patients have circulatory failure. Threshold for overdistension is unknown, but it may be more likely at mPaw > 35 cmH<sub>2</sub>O.

**Monitor:** SpO<sub>2</sub> or PaO<sub>2</sub>; Observe SpO<sub>2</sub> changes 5–10 minutes after a change in ventilator settings. Check ABG twice daily.  
**Target:** PaO<sub>2</sub> 55–80 mmHg or SpO<sub>2</sub> 88–95%; use PaO<sub>2</sub> for decisions if only one is out of target range.

#### Initial settings and adjustments:

- mPaw = mPaw on conventional ventilator + 5 cmH<sub>2</sub>O, but do not exceed 35 cmH<sub>2</sub>O
- FiO<sub>2</sub> = 1.0
- If oxygenation is below target, increase mPaw in 5 cmH<sub>2</sub>O increments to maximum of 45 cmH<sub>2</sub>O. Consider recruitment 1–2 maneuvers.<sup>2</sup>
- If oxygenation is above target, decrease FiO<sub>2</sub> to reach a FiO<sub>2</sub>/mPaw combination on scale

#### Subsequent adjustments:

##### Oxygenation in target range

- No change required

##### Oxygenation above the target range

- Decrease down FiO<sub>2</sub>/mPaw scale in 1–2 step increments

##### Oxygenation below target range

- Increase up FiO<sub>2</sub>/mPaw scale in 1–2 step increments (Consider recruitment maneuvers) (Higher mPaws may depress venous return; assure adequate volume.) (At mPaw > 35 or FiO<sub>2</sub> > 0.9, consider prone positioning or iNO)

<sup>2</sup> A recruitment maneuver consists of stopping oscillator and elevating mPaw to 45 cmH<sub>2</sub>O. Maintain for 40–60 seconds. Monitor closely for hypotension or desaturation. Return to desired settings and restart oscillator.

### mPaw/FiO<sub>2</sub> Scale for HFOV

Adjust FiO<sub>2</sub> or mPaw according to the scale to maintain oxygenation in target range

(for patients without circulatory failure)

FiO <sub>2</sub>	.40	.40	.50	.50	.60	.70	.80	.90	.90	.90	1.0	1.0
mPaw	20	25	25	30	30	30	30	30	35	40	40	45

(for patients with circulatory failure)

FiO <sub>2</sub>	.40	.50	.60	.60	.70	.80	.80	.90	.90	1.0	1.0	1.0
mPaw	20	20	20	25	25	25	30	30	35	35	40	45

### Worsening Arterial Oxygenation → ← Improving Arterial Oxygenation

- Oxygenation Goals: Oxygen Saturation 88–95% or PaO<sub>2</sub> 55–80 mmHg
- Circulatory failure = mean arterial pressure < 60 mmHg or vasopressors; note that CVP 15–20 mmHg may be needed to achieve adequate RV filling.

Figure 1. The HFOV Quick Guide is a chart summarizing the protocol for clinical application of high-frequency oscillatory ventilation (HFOV) used at Johns Hopkins Hospital. It is posted at the bedside of all patients on HFOV as a reference for housestaff, nurses, and respiratory therapists. Greater detail is available in the protocol manuals for nursing and respiratory therapy.

be smaller at higher frequency even with higher delta P. Applying this approach to our last nine patients, we found that six could maintain pH >7.25 at frequencies between 7 and 12 Hz. The other three required frequencies of 3–4 Hz as a result of refractory acidosis.

**Mean Airway Pressure.** The mPaw should be maintained in the 25- to 35-cm H<sub>2</sub>O range to promote lung recruitment, but FiO<sub>2</sub> should be increased instead of mPaw to maintain oxygenation when blood pressure is compromised.

**Recruitment Maneuvers.** Attempts to

recruit lung by briefly (~1 min) raising mPaw to 40–50 cm H<sub>2</sub>O may be attempted when initiating HFOV or after suctioning or patient disconnections. We know of no clinical data to support the use of recruitment maneuvers at regular intervals or repeated attempts in patients who fail to demonstrate a brisk and sustained improvement in oxygenation after a maneuver.

**Transition to Conventional Ventilation.** To minimize the duration of HFOV, patients in whom HFOV is used as rescue therapy for gas exchange should have a

trial of conventional ventilation daily when gas exchange improves to require a  $mPaw < 30$  cm H<sub>2</sub>O and  $< 50\%$  oxygen. Transition criteria will differ for research patients in whom HFOV is applied early in their course to study its effect on ventilator-induced lung injury. In that situation, a minimum duration of HFOV may be required. In addition, lung mechanics and gas exchange should improve to the point where the risk of substantial ventilator-induced injury on conventional ventilation will be low. This might be indicated by a plateau pressure  $< 25$  cm H<sub>2</sub>O, need for  $< 50\%$   $F_{iO_2}$ , and a minute ventilation  $< 12$  L during a trial on conventional, lung-protective ventilation.

**Sedation.** To minimize the total duration of mechanical ventilation, sedation, and neuromuscular blockade on both HFOV and conventional ventilation should be controlled by a separate protocol. See chapter 16 of this supplement.

The introduction of an endotracheal tube cuff leak can also be used to improve CO<sub>2</sub> clearance during HFOV. This will allow the use of lower tidal volumes, potentially improving the degree of lung protection. However, deflating the endotracheal tube cuff may also promote ventilator-associated pneumonia by allowing oral secretions to enter the lower airways. We have no data on which to base a recommendation as to when a cuff leak should be added in a management algorithm. However, rules for a cuff leak should be designed into a research protocol so that its use will be consistent and reproducible.

Currently, we use HFOV for patients failing conventional lung-protective ventilation. Our *clinical* protocol for HFOV is summarized in Figure 1.

## CONCLUSIONS

Well-designed management protocols are essential for interpretable clinical trials and have been shown to improve numerous aspects of care for the critically ill. Protocol development can be arduous but can yield the returns of more efficient and effective patient care. Protocol development for HFOV is in its formative stage, hampered by limited human physiological data and the inability to measure tidal volume. These protocols will mature with improved instrumentation

(see chapters 10 and 11), focused pilot studies, and consensus-building among experienced users. We will then be prepared to undertake a clinical efficacy trial, the results of which can be definitive and robust.

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