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SPECIAL FEATURE

Acute Kidney Failure and Renal Replacement Therapy in the ICU: A Review

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Dr. Tran reports no financial relationships relevant to this field of study.

Acute renal failure (ARF) necessitating renal replacement therapy (RRT) is a common complication in the ICU, and one associated with high mortality and demand on clinical resources. In an effort to recognize injury to the kidney that may not result in "failure" but also has significant clinical implications, the term "acute kidney injury" (AKI) is increasingly preferred by the nephrology and ICU communities.[1] This special feature aims to review the definition and scope of this complication in the ICU and discuss available RRT strategies in terms of the advantages/disadvantages of various modes, dose, and timing.

DEFINITION

There are three commonly encountered definitions for AKI. First, in 2004, the Acute Dialysis Quality Initiative (ADQI) published a consensus definition and classification scheme for AKI in the hopes of standardizing studies aimed at its prevention and treatment. Second, the RIFLE criteria defined AKI as an increase in serum creatinine (SCr) of ≥ 50% developing over ≤ 7 days, or a decrease by ≥ 25% in glomerular filtration rate (GFR), or urine output < 0.5 mg/kg/hour for ≥ 6 hours. The RIFLE acronym summarizes the categories of Risk, Injury, Failure, Loss, and End-stage disease, based on degree of SCr, GFR, and urine output changes (*see Table 1*).[2]

Finally, because even small rises in creatinine of as little as 0.3-0.4 mg/dL were subsequently found to be associated with a 70% increase in mortality risk (95% confidence interval [CI], 1.2-2.6),[3] the RIFLE criteria were later refined by the international Acute Kidney Injury Network (AKIN) in an effort to increase sensitivity in AKI diagnosis and its earlier detection. The AKIN criteria are similar to RIFLE in terms of SCr change and urine output definitions, but discarded the GFR criteria given absence of readily available methods to measure GFR

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Table 1. RIFLE vs AKIN and KDIGO Classification for Acute Kidney Injury

Category	Serum Creatinine (SCr) Criteria	Urine Output Criteria
RIFLE		
Risk	Increase in SCr ≥ 1.5x baseline, or decrease in GFR ≥ 25%	< 0.5 mL/kg/h for ≥ 6 hours
Injury	Increase in SCr ≥ 2.0x baseline, or decrease in GFR ≥ 50%	< 0.5 mL/kg/h for ≥ 12 hours
Failure	Increase in SCr ≥ 3.0x baseline, or decrease in GFR ≥ 75%	< 0.3 mL/kg/h for ≥ 24 hours, or anuria ≥ 12 hours
AKIN/KDIGO		
Stage 1	Increase in SCr ≥ 0.3 mg/dL (26.2 µmol/L), or increase to ≥ 150-199% (1.5-1.9-fold) from baseline	< 0.5 mL/kg/h for ≥ 6 hours
Stage 2	Increase in SCr to 200-299% (2-2.9-fold) from baseline	< 0.5 mL/kg/h for ≥ 12 hours
Stage 3	Increase in SCr to ≥ 300% (3-fold) from baseline, or SCr ≥ 4.0 mg/dL (354 µmol/L) with an acute rise ≥ 0.5 mg/dL (44 µmol/L), or initiation of RRT	< 0.3 mL/kg/h for ≥ 24 hours, or anuria ≥ 12 hours

Adapted from Bagshaw SM, et al.[5] (AKI = Acute Kidney Injury; for other definitions see text.)

(*see Table 1*). AKIN also modified the definition of AKI to be an abrupt (within 48 hours) change, and emphasized that the criteria should only be applied after volume status had been optimized and urinary tract obstruction excluded if using the urine output criteria.

The Kidney Disease/Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI retained all the AKIN definitions and staging criteria but also included the original ≥ 50% increase in SCr within 7 days criterion from RIFLE (*see Table 1*).[4] When applied in practice, there were no significant differences in the incidence or outcomes of AKI by using the AKIN as opposed to the RIFLE criteria,[5] and both classification schemes in addition to KDIGO are recognized by multiple medical societies and used in clinical studies.

EPIDEMIOLOGY AND OUTCOMES

In a large, international cohort of 29,269 critically ill patients in 23 countries, the BEST (Beginning and Ending Supportive Therapy for the Kidney) study reported a period prevalence for ARF of 5.7% (range, 1.4-25.9%).[6] Septic shock was the most common contributing factor and was seen in 47.5% of all patients with ARF. Hospital mortality for patients with ARF was 60.3% (95% CI, 58.0-62.6%), with 52% of patients dying in the ICU setting.[6] The investigators used a simpler definition of ARF in an effort to identify patients who would likely trigger initiation of RRT in the ICU: 1) urine output < 200 mL in 12 hours, and/or 2) blood urea nitrogen level > 84 mg/dL (> 30 mmol/L). Although other studies have used different definitions of ARF, their estimates of prevalence and ICU/hospital mortality are quite similar.[7-9] Risk factors for AKI are well established but are often broad and immutable such that they do not provide opportunities for many preventive trials; these include age, sepsis, cardiac surgery, intravenous contrast, diabetes, rhabdomyolysis, pre-existing renal disease, hypovolemia, and shock.[1]

In general, the more severe the kidney injury, the higher the short- and long-term mortality risk associated with it. In 5383 ICU patients at a single center, patients with AKI in RIFLE class R, I, and F had hospital mortality rates of 8.8%, 11.4%,

Table 2. Common Modes of Renal Replacement Therapy		
RRT Modality	Transport Principle	Characteristics
IHD	Diffusion	"Classic" hemodialysis
SLEDD	Diffusion	Uses IHD machine; slower blood and dialysate flows than IHD; longer RRT times; more hemodynamic stability
CVVHD	Diffusion	Continuous hemodialysis at slower dialysate flow rates (1-1.2 L/hour)
CVVH	Convection	"Classic" hemofiltration
SCUF	Convection	No solute removal; good for large volume removal; no dialysate or replacement fluids needed
AVVH	Convection	Higher flow rates than CVVH (350-400 mL/min); shorter RRT times; no anticoagulation needed
CVVHDF	Convection and diffusion	Continuous hemofiltration combined with diffusive dialysis at low flow rates; effective small and middle molecule solute clearance; both dialysate and replacement fluids required

RRT = Renal Replacement Therapy; IHD = intermittent hemodialysis; SLEDD = slow low-efficiency daily dialysis; CVVHD = continuous venovenous hemodialysis; CVVH = continuous venovenous hemofiltration; SCUF = slow continuous ultrafiltration; AVVH = accelerated venovenous hemofiltration; CVVHDF = continuous venovenous hemodiafiltration.
Adapted from John S, Eckardt KU.[16]

and 26.3%, respectively, compared to 5.5% for patients without AKI.[10] In a larger study using AKIN criteria with a 2-year follow-up, patients with AKIN 1, AKIN 2, and AKIN 3 stages had increasing 60-day as well as 2-year mortality risks at 1.19, 1.17, and 1.53, respectively ($P < 0.001$ for all) compared to patients with no AKI.[11] Additional studies have also reported decreased survival even at 5 and 10 years in patients with mild AKI (KDIGO stage 1) compared to no AKI.[12]

Although AKI is a significant risk factor for death in multivariable analyses, it is important to remember that these associations do not necessarily imply a cause and effect relationship. Although it is theoretically possible that renal dysfunction can lead to severe pathophysiologic derangements such as volume overload, acid-base problems, alterations in innate immunity, increased risk for infection, and an overall pro-inflammatory state, it is possible that AKI is simply a surrogate marker for increased morbidity and mortality in the ICU.[10]

METHODS AND MODES FOR RRT

The most common and contrasted methods for RRT are intermittent hemodialysis (IHD) and continuous venovenous hemofiltration (CVVH). Hemodialysis is based on diffusion, whereby the presence of a concentration gradient drives solutes across a semi-permeable membrane between blood and the dialysate. High dialysate flow rates are required (~500 mL/min). IHD is highly effective at removing small molecules, which allows for intermittent treatments and is advantageous in many acute, potentially life-threatening conditions such as hyperkalemia, rhabdomyolysis, tumor lysis syndrome, and certain poisonings. Other advantages of IHD include low cost and the possibility of performing it without anticoagulation. However, given the rapid reduction in plasma osmolality that causes extracellular water to move into cells and rapid fluid removal, it may not be well tolerated in patients who are hypotensive.

Hemofiltration, on the other hand, relies on convection, whereby positive hydrostatic pressure (rather than a concentration gradient) drives both water and solutes across a semi-permeable membrane from blood to filtrate. Both small and middle-sized molecules are cleared, and the volume of the filtrate has to be continuously substituted by replacement fluids. In contrast to IHD, hemofiltration is delivered continuously for 18-24 hours/day at slower rates (1-3 L/hour), although it can be used intermittently if higher ultrafiltration rates are applied. Its theoretical advantages, however, include more hemodynamic stability allowing for more adequate fluid removal and better recovery of renal function, as well as clearance of mid-size molecules such as cytokines.[13] On the other hand, it requires continuous anticoagulation and involves continuous exposure to an extracorporeal circuit that may lead to nutrient depletion, sub-therapeutic levels of antibiotics, and infection.[13]

Numerous studies, including randomized trials, comparing intermittent to continuous RRT have failed to find consistent results showing one

mode is superior to another in terms of clinically important outcomes such as survival rates and renal recovery.[14,15] However, given the inherent advantages and disadvantages of each mode, there is significant heterogeneity in the ICU populations that received each type of RRT, which make comparisons difficult. RRT modes, therefore, may not be interchangeable in individual patients and should be selected based on actual clinical conditions. Hybrid techniques employing aspects of both IHD and CVVH have been used, including slow, low-efficiency daily dialysis (SLEDD), which combines the theoretical advantages of both IHD and CRRT (*see Table 2*).[16] Major outcome trials comparing these hybrid techniques to more traditional approaches in large populations are currently lacking.

DOSE OF RRT

Quantification of urea removal is commonly used in evaluating RRT efficiency and comparing dialysis dosing. For IHD, this is the Kt/Vd measurement (K: dialyzer clearance of urea, t: duration of dialysis, Vd: urea distribution volume), whereas for hemofiltration, it is equal to the rate of ultrafiltration.

Prior to 2008, randomized controlled trials investigating the effect of RRT dose on mortality and renal function recovery reported mixed results, with some trials suggesting a survival benefit with more intense RRT. The largest, best-designed trials looking at the optimal intensity of RRT among critically ill patients have since found no benefit with higher intensity compared to less intensive regimens. The Acute Renal Failure Trial Network randomized 1124 patients with ARF to either a high intensity (IHD or slow, low-efficiency dialysis six times/week or CVVH at 35 mL/kg/hour, depending on hemodynamics) or less intensive strategy (IHD or slow, low-efficiency dialysis three times/week or CVVH at 20 mL/kg/hour); each IHD or slow, low-efficiency dialysis session provided a dose (Kt/Vd) of 1.2-1.4 per session.[17] Sixty-day mortality was similar between the two groups (53.6% high intensity group vs 51.5% less intensive group, odds ratio [OR], 1.09; P = 0.47) with no significant difference in rate of renal recovery.[17]

Similarly, the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study, which enrolled 1508 patients from Australia and New Zealand who were critically ill and receiving CVVH to a higher intensity (40 mL/kg/hour) vs lower intensity (25 mL/kg/hour) regimen, found no difference in 90-day mortality (44.7% in both groups; OR, 1.00; P = 0.99) or rates of renal recovery.[18] Based on these studies and prior knowledge that inadequate dialysis has been associated with higher mortality rates in chronic renal failure,[4] we can conclude that: 1) RRT doses are important, 2) at least 3.6 Kt/Vd for IHD or SLEDD and 20 mL/kg/h are likely adequate for most critically ill patients requiring RRT for ARF, and 3) increases beyond an adequate level of intensity provide no additional benefit.[1]

INDICATIONS AND TIMING OF RRT

Although the absolute indications for RRT in critically ill patients are often agreed on (metabolic acidosis, hyperkalemia, and/or hypervolemia that do not respond to medical therapy), the optimal timing ("early" vs "late") to initiate RRT remains unanswered. In general, studies have shown no significant survival benefit or improved chance of renal recovery with earlier commencement of RRT relative to onset of AKI.[19,20] However, the risk of death does appear to rise in a graded fashion with progressive delay of RRT, suggesting that further studies are warranted in assessing the role of RRT timing in AKI.[20,21] At the other end of the spectrum, "prophylactic" RRT in the absence of renal injury has been ineffective in studies in patients with trauma and septic shock in terms of improving the risk or severity of organ dysfunction.[16]

CONCLUSION

AKI contributes substantially to the morbidity and mortality of critically ill patients. RRT can provide renal support via a variety of modes, all of which have advantages and disadvantages depending on the individual clinical scenario. Although we have learned that adequate RRT dosing is necessary, many questions remain with regard to the optimal dosing and timing of RRT initiation. As no one mode has been shown to have a survival advantage over another, collaboration between the nephrologist and intensivist is vital to develop a RRT strategy that is appropriate and in keeping with the patient's medical treatment plan. ■

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ABSTRACT & COMMENTARY

Conservative Fluid Management Reduces the Incidence of VAP

By Richard H. Kallet, MS, RRT, FAARC, FCCM

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Mr. Kallet reports no financial relationships relevant to this field of study.

SYNOPSIS: Patients on mechanical ventilation who were managed with both conservative fluid administration and aggressive diuresis weaned faster, had significantly more ventilator-free days, and experienced reduced incidences of both ventilator-associated complications and ventilator-associated pneumonia.

SOURCE: Mekontso Dessap A, et al. Ventilator-associated pneumonia during weaning from mechanical ventilation: Role of fluid management. *Chest* 2014; Mar 20. doi: 10.1378/chest.13-2564. [Epub ahead of print.]

This article reports a secondary analysis of patients enrolled into a multicenter, randomized, controlled trial that examined the impact of B-type natriuretic peptide (BNP)-directed fluid management ("fluid-depletion strategy") vs "usual care."[1] The relationship between fluid balance and the incidence of ventilator-associated pneumonia (VAP) over the first 14 study days was analyzed in patients who met weaning-readiness criteria. Weaning was standardized using an automated pressure-support titration algorithm. When daily BNP values were ≥ 200 pg/mL, patients in the fluid-depletion arm had fluid restriction (baseline infusion ≤ 0.5 L/day; parental nutrition ≤ 1 L/day) along with aggressive diuresis (furoseminde: 10-30 mg boluses, Q-3h), targeting a urine output of 4.5-9 mL/kg over 3 hours. In the usual care group, clinicians were blinded to the BNP results, and both fluids and diuretics were administered per clinician practice. VAP diagnosis was standardized and required positive quantitative cultures from distal pulmonary sampling.

The 304 medical-surgical patients studied (152 in each group) were not different in terms of baseline characteristics and risk factors for VAP, and they had been receiving mechanical ventilation (MV) for approximately 4-5 days at randomization. There was a significantly lower incidence of VAP in the BNP-managed group (8.6%) vs the usual care group (17.8%, $P = 0.03$). This also coincided with a more negative daily fluid balance, faster weaning time, and more ventilator-free days.

■ COMMENTARY

Both the parent trial[1] and the seminal NIH FACTT study[2] have validated the emerging concept that "keeping the lungs dry" during critical illness improves outcomes, in part by reducing the need

for MV. The current study augments these findings by showing that reducing the need for MV provides an additional benefit of decreasing the incidence of VAP. Patients in the BNP group were successfully weaned approximately 1 day earlier (27 hours) than those in the usual care group, and on average were successfully extubated < 48 hours into the trial. The most obvious explanation is that the lower incidence of VAP stems from reduced risk exposure related to the presence of the endotracheal tube.

Because the duration of MV is a risk for VAP (and VAP increases the duration of MV), the investigators used a competing risk model to analyze the effects of the fluid-depletion strategy while controlling for weaning outcome. They found that the fluid-depletion strategy itself significantly reduced the risk of both ventilator-associated complications and VAP (sub-hazard ratios of 0.44 (P = 0.02) and 0.50 (P = 0.03), respectively). These findings lead the authors to speculate that pulmonary edema may exert an independent risk for developing VAP by two mechanisms: 1) the long-recognized impairment of pulmonary host-defense mechanisms, and 2) an interesting hypothesis of enhanced growth and virulence of *Pseudomonadaceae* because these bacteria characteristically thrive in wet conditions. In this study, *Pseudomonadaceae* accounted for 44% of all positive bronchoalveolar lavage fluid cultures. The independent effect of pulmonary edema on VAP is an enticing explanation as some of the highest at-risk patients are those suffering from acute respiratory distress syndrome, traumatic injuries, and massive burns, conditions commonly associated with large fluid requirements and pulmonary edema formation.

This study underscores the beneficial effects of fluid restriction and aggressive diuresis in critically ill patients *once they have achieved hemodynamic stability*. Despite the growing body of evidence supporting this approach, it has not been enthusiastically embraced, particularly in the management of trauma patients. Unarguably, persistent hypotension caused by sustained capillary leak is a daunting problem. But overzealous crystalloid therapy also has been a well-recognized problem for more than 70 years, and one that "every generation of surgeons must discover for themselves."[3] However, with mandatory public reporting of ventilator-associated complications looming in the near future, complacency toward managing "correctable" risk factors leading to avoidable patient complications will not be tolerated by society. The cumulative evidence clearly suggests that much more can be done to improve this aspect of patient care. ■

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ABSTRACT & COMMENTARY

Effects of High-Flow Nasal Cannula vs Conventional Oxygen Therapy in Recently Extubated Patients

By David J. Pierson, MD, Editor

SYNOPSIS: This short-term crossover study showed that in the first hour after extubation, patients were less dyspneic and had lower respiratory and heart rates while breathing oxygen via high-flow nasal cannula than with a conventional non-rebreathing mask.

SOURCE: Rittayamai N, et al. High-flow nasal cannula versus conventional oxygen therapy after endotracheal extubation: A randomized crossover physiologic study. *Respir Care* 2014;59:485-490.

This study from Siriraj Hospital in Bangkok sought to determine whether the use of a high-flow nasal cannula (HFNC) system to deliver oxygen to patients following extubation had physiological advantages over a traditional non-rebreathing mask. The authors selected 17 patients recovering from acute respiratory failure (mean age 67 years, 41% female) whose acute illness requiring invasive mechanical ventilation was precipitated evenly among chronic obstructive pulmonary disease exacerbations, pneumonia, and other etiologies. After improving from the acute episode, the patients had to meet usual criteria for weaning and pass a 120-minute spontaneous breathing trial on either a T-piece or

low-level pressure support. Once informed consent for the study was obtained, patients were extubated and then placed randomly either on HFNC or a non-rebreathing mask for 30 minutes. After measurement of respiratory and heart rates and quantitation of dyspnea using a 10-point analog scale, the patients were then switched to the other mode of oxygen delivery and the assessments were repeated after another 30 minutes. HFNC was delivered at 35 L/min, with FIO_2 sufficient to maintain SpO_2 94% or more. Oxygen was delivered to the non-rebreathing mask at 6-10 L/min to maintain the same saturation. Patients randomized to the two oxygen delivery sequences did not differ statistically with respect to the demographic or clinical variables assessed, and all of them remained extubated without the need for reintubation. Noninvasive ventilation was not used.

Nine patients received HFNC first and switched after 30 minutes to a non-rebreathing mask; eight patients had this sequence reversed. By the scores in the visual analog scale, the patients had less dyspnea with HFNC (P = 0.04) and subjectively 88% of them preferred the HFNC to the non-rebreathing mask. Their respiratory and heart rates during the 30-minute sessions were significantly lower with the HFNC: 19.8 ± 3.2 vs 23.1 ± 4.4 breaths/min (P = 0.009) and 89.5 ± 9.5 vs 95.4 ± 10.4 (P = 0.006) beats/min, respectively. Two patients reported subjective discomfort ("gas flow too high" and "temperature too warm") with HFNC in comparison with the non-rebreathing mask, but no serious adverse events occurred.

■ COMMENTARY

The development of HFNC, its rationale, and its reported effects (documented mainly in neonates and young children) have recently been reviewed by Ward.[1] More directly pertinent to readers of this newsletter is a special feature published last year by Walter[2] that summarized what we know about the potential value of HFNC in adult critical care. Walter pointed out that HFNC is relatively easy to use, appears to fill a niche between low-flow nasal cannula/face mask systems and noninvasive ventilation, and has the advantage of allowing patients to talk, eat, drink, and more easily clear secretions compared to noninvasive ventilation.[2] However, he also cautioned that, like so much of the technology of critical care, HFNC has been widely adopted by clinicians on the basis of plausible rationale and effective marketing in advance of definitive research to show whether its claimed clinical benefits are real.

The findings from this and other studies to date support the postulated mechanisms for improved gas exchange and ventilatory mechanics with HFNC as compared with low-flow nasal or non-rebreathing mask oxygen. These are the substantially increased flow (which can better match patients' peak inspiratory flows during spontaneous breathing), the creation of a better reservoir of oxygen in the upper airway during expiration (which would increase lower-airway oxygen concentration and perhaps serve to reduce dead space), and the promotion of continuous positive airway pressure (CPAP) because of the high flow (something of a misnomer since the pressure may not actually remain positive throughout inspiration). A CPAP effect would theoretically increase functional residual capacity and thus might reduce patient work of breathing, although as Rittayamai et al point out in their discussion the available data suggest that HFNC produces only 1.5-7.0 cm H_2O of positive airway pressure.

A sound rationale is important but does not by itself establish the clinical value of a device or intervention, and the current study takes us a little bit closer to the patient-relevant evidence we need. It suggests using noninvasive bedside assessments during the first hour after removal of the endotracheal tube — among patients who have already met current best-practice criteria for extubation — that spontaneous breathing was more effective and comfortable with HFNC than with a non-rebreathing mask. However, this was a short-term physiologic study with only 17 low-risk patients, none of whom required reintubation or had other adverse extubation outcomes.

Hopefully, the clinical study we really need on HFNC after extubation (that is, compared to other support, will it reduce the need for reintubation) will be performed soon. In the meantime, clinicians should keep two things in mind: Although patients tolerate it well, the effects of HFNC on ventilation remain unknown (and the current study's short-term findings could actually be compatible with decreased spontaneous ventilation); and, recently extubated patients still need close monitoring in the ICU. At this point, HFNC should not be used as a means for getting patients recovering from acute respiratory failure out of the ICU faster, particularly within the first 24 hours after extubation. ■

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CME QUESTIONS

1. Which of the following is a characteristic of hemodialysis?
   a. It does not require anticoagulation.
   b. High dialysate flows are required.
   c. It is highly efficient at removing small molecules.
   d. Solutes are removed via diffusion.
   e. All of the above

2. Which of the following statements is true regarding modality, dose, and timing of renal replacement therapy (RRT) in the ICU?
   a. Continuous venovenous hemofiltration is superior to intermittent hemodialysis regarding renal recovery.
   b. Continuous venovenous hemofiltration is superior to intermittent hemodialysis regarding ICU survival.
   c. Found no benefit with higher intensity compared to less intensive regimens.
   d. Earlier initiation of RRT is associated with an increased chance of renal recovery.

3. Which of the following statements is *false* regarding patients in the study evaluating fluid management and ventilator-associated pneumonia (VAP)?
   a. Patients had been ventilated for an average of 4-5 days at randomization.
   b. Daily BNP levels ≥ 200 pg/mL were treated with 10-30 mg furosemide Q-3 h.
   c. All patients were weaned using a closed-loop pressure-support ventilation algorithm
   d. The incidence of VAP was significantly reduced in the "fluid-depletion" arm.
   e. Findings indicated no difference in duration of mechanical ventilation or in the incidence of ventilator-associated complications.

4. In the study by Mekontso Dessap et al, which of the following hypotheses has *not* been proposed to explain a reduced incidence of VAP associated with fluid depletion?
   a. Pulmonary edema improves pulmonary defense mechanisms by enhancing bacteriocidal properties of pulmonary macrophages.
   b. Diuresis improves oxygenation so that patients meet weaning readiness criteria earlier.
   c. Diuresis improves pulmonary compliance, which reduces patient work of breathing and thereby facilitates weaning.
   d. Reduced pulmonary edema makes a less hospitable environment for pseudomonas growth.
   e. Reduced pulmonary edema preserves pulmonary host defenses.

5. Which of the following is a possible explanation for the effectiveness of high-flow nasal cannula, in comparison with mask oxygen, in managing patients following extubation?
   a. Better matching of patients' peak inspiratory flows
   b. Positive airway pressure created by the high nasal flow
   c. Increased upper airway oxygen reservoir
   d. Decreased work of breathing
   e. All of the above