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SPECIAL FEATURE

Clinical Application of Biomarkers of Acute Kidney Injury in the ICU

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Biomarkers have become an important tool for the early recognition and prognostication of acute kidney injury (AKI). The use of traditional markers (creatinine and urine output) is associated with poor sensitivity for early recognition or for determination of the extent and location of the renal injury (glomeruli or tubules). In addition, these traditional biomarkers are insufficient to determine renal recovery or to provide long-term prognosis. In the last few years, several biomarkers have emerged that have shown promising results in large-scale clinical studies.

Creatinine derived from creatine, a waste product from muscle metabolism, typically is cleared by glomerular filtration and by proximal tubular secretion. Although creatinine often is used clinically as a marker of renal function, there are several limitations to consider in the setting of AKI. First, creatinine requires time to accumulate, and elevation may not be seen until 24-48 hours after a renal insult has already occurred.[1] Second, in patients with normal renal reserve, changes in serum creatinine may not be seen in acute injury that involves less than 50% of the nephrons, given the compensatory response of the remaining nephrons.[2] In addition, the amount of tubular secretion becomes an increasingly important fraction of excreted creatinine inverse to the amount excreted through glomerular filtration. As such, the accumulation of creatinine does not occur in a linear fashion with reduced glomerular filtration. Also, several confounding factors can affect serum creatinine. The serum creatinine can overestimate an acute reduction in the glomerular filtration rate (GFR) in chronic kidney disease (CKD), in rhabdomyolysis, and with the use of medications that block tubular creatinine secretion (e.g., cimetidine, trimethoprim). Serum creatinine can underestimate a reduction in GFR

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in patients with low muscle mass, poor nutritional status, and volume overload, such as those with cirrhosis or congestive heart failure.[3] Fourth, sepsis, the most common cause of AKI in the intensive care unit (ICU), reduces energy production and lowers muscle perfusion, which subsequently can result in a delay in serum creatinine elevation.[4] Finally, baseline serum creatinine is always necessary to evaluate for the presence of AKI; however, many patients may not have such data available at the time of hospital admission.[5]

Reduced urine output (UOP) is considered to be a more sensitive marker for AKI diagnosis than serum creatinine because urine production is directly influenced by the GFR reduction. However, similar to creatinine, UOP is not specific for AKI. Oliguria can be induced by multiple physiologic factors, such as hypovolemia, prolonged fasting, fever, sepsis, acute ischemic stroke, acute coronary syndrome, or uncontrolled pain. The common mechanism for these conditions is increased sympathetic activity leading to increased release of antidiuretic hormone. Urinary tract obstruction is another common extrarenal factor decreasing UOP.[6] In contrast, UOP can persist until GFR nears zero in non-oliguric AKI, such as in nephrotoxin-induced AKI or leptospirosis.[7] Weight-adjusted UOP criteria can be misleading in obese patients, and some reports have suggested that using ideal body weight instead of true weight might be more appropriate to avoid overdiagnosing AKI in the obese population.[6]

AKI should be considered a continuum that starts with kidney stress and progresses to early injury that then extends, resulting in renal dysfunction with either subsequent full recovery/repair, established non-reversible damage (i.e., end-stage renal disease [ESRD]), or partial recovery leading to CKD. At each point on the continuum, biomarkers may help define the mechanisms and predict the course of AKI.[6] The discovery of renal biomarkers has been difficult due to the multiple conditions and different mechanisms responsible for AKI. Biomarkers can be classified into two main categories: indicators of damage and indicators of dysfunction.

Only a few biomarkers of renal damage and dysfunction have been approved by the Food and Drug Administration (FDA) for clinical implementation as a diagnostic or predictive tool in AKI. These biomarkers include Cystatin C (CysC), tissue inhibitor of metalloproteinases-2 (TIMP2), and insulin-like growth factor-binding protein 7 (IGFBP7), which have shown consistent results in several clinical situations (e.g., prediction of AKI, prediction of need for renal replacement therapy [RRT], and prediction of long-term outcomes such as mortality, and prognosis of AKI) related to acute renal dysfunction.[8,9] Neutrophil gelatinase-associated lipocalin (NGAL) is another biomarker of renal injury that has been extensively studied and is currently approved by the FDA for use in the pediatric population and is under evaluation for implementation in adults. The combination of TIMP2 and IGFBP7 is commercially available and approved by the FDA as a rapid urine test called NephroCheck. Another prognostic tool that deserves special consideration in the ICU is the use of a furosemide stress test (FST), a functional test that evaluates the integrity of the tubular system after a loading dose of furosemide in patients with early AKI.[10]

PREDICTION OF ACUTE KIDNEY INJURY

NGAL. NGAL has been found to be a good predictor of AKI in critically ill patients, in kidney transplant patients, and after cardiac surgery. It rises in proportion to renal injury severity and duration; it is expressed early, within one to three hours of renal insult and 36-72 hours before an increase in creatinine; it is measured in urine or plasma; and it can be assayed rapidly. Urinary NGAL may have higher specificity than plasma for AKI.[9] Ho and colleagues conducted a meta-analysis of NGAL's ability to predict AKI after cardiac surgery and found the area under the receiver operating characteristic curve (AUROC) for urinary NGAL and plasma NGAL to be 0.72 and 0.71, respectively.[11] In addition, a multicenter prospective study of 1,635 patients showed that a single measurement of urinary NGAL in the

emergency department had better discriminatory ability to predict intrinsic AKI (AUCROC of 0.81) than other biomarkers.[12] In a meta-analysis of 2,538 patients (19 studies from eight countries) that used a uniform creatinine-based definition of AKI (Cr increase > 50% within seven days), the AUROC for plasma NGAL for predicting AKI across all settings was 0.83 when using a median cutoff value of > 150 ng/mL.[13]

Cystatin C (CysC). CysC is a 13-kDa cysteine protease inhibitor that is produced by all human nucleated cells at stable production rates. Few situations can affect CysC production, including advanced age, systemic inflammation (e.g., sepsis), and a high dose of glucocorticoids. Because CysC is filtered freely through the normal glomerulus and then completely reabsorbed by proximal tubule cells, it is absent in the urine. CysC has been studied as a marker of GFR by measuring it in serum. Compared with serum creatinine, serum CysC is more sensitive to early renal dysfunction, and elevated urinary CysC may suggest tubular injury and could be a marker of AKI.[14] Herget-Rosenthal et al[15] reported an increase in serum CysC by more than 50% occurred 0.6 days earlier compared to serum creatinine as a way to detect AKI (AUROC 0.92-0.98) in a cohort of 85 ICU patients. Similarly, in another ICU cohort, plasma CysC increased 18-24 hours earlier than creatinine and predicted sustained AKI with an AUROC of 0.80.[16]

Tissue Inhibitor of Metalloproteinases-2 (TIMP2) and Insulin-Like Growth Factor-Binding Protein 7 (IGTBP7). In the initial validation study, urinary TIMP2-IGFBP7 was superior to all existing biomarkers in predicting progression of AKI to stage 2 or 3 based on Kidney Disease: Improving Global Outcomes (KDIGO) score within 12 hours of sample collection with an AUROC of 0.80 in a heterogeneous group of patients, including those with sepsis, shock, trauma, and major surgery.[17] The initial results have been confirmed subsequently by various cohorts. Although most of the studies for urinary TIMP2-IGFBP7 enroll a cardiac surgery population, it has been shown to perform well in patients with sepsis (AUROC 0.85), post-surgery (AUROC 0.84), with congestive heart failure (AUROC 0.89), and with CKD (AUROC 0.91). The test has been shown to detect kidney stress rapidly (within four hours after exposures) and to predict subsequent occurrence of AKI accurately at the cutoff of 0.3 $(ng/mL)^2/1,000$.

PROGNOSIS OF ACUTE KIDNEY INJURY

Furosemide Stress Test. The furosemide stress test (FST) is used to assess the integrity of tubular function in the setting of AKI. This test was studied initially by Chawla et al in 77 ICU patients with early oliguric AKI who received a single intravenous dose of furosemide (1 mg/kg for furosemide-naïve patients or 1.5 mg/kg for patients with prior furosemide use). The study demonstrated that two-hour urine output < 200 mL in response to a furosemide challenge was able to predict progression to stage 3 AKI or need for RRT (AUROC 0.87, sensitivity 87%, specificity 84%).[10]

NGAL. Urinary NGAL can be used to distinguish intrinsic AKI (i.e., acute tubular necrosis, or ATN) from pre-renal azotemia, defined as renal dysfunction responsive to fluid resuscitation and hemodynamic optimization, with an AUROC of 0.87 in hospitalized patients.[18] Recently, a prospective study in ICU patients reported the predictive ability of urinary NGAL (cutoff 80 ng/mL) and plasma NGAL (cutoff 150 ng/mL) for persistent AKI with AUROCs of 0.83 and 0.85, respectively.[19] Furthermore, normalized urinary NGAL (at a cutoff of 110 µg/g creatinine) obtained on the day of AKI diagnosis has been reported to have the ability to distinguish between ATN, prerenal, and hepatorenal syndrome with an AUROC of 0.80 in a cohort of 320 hospitalized cirrhotic patients with AKI.[20]

PREDICTION OF RENAL REPLACEMENT THERAPY AND LONG-TERM OUTCOMES

Furosemide Stress Test. FST was significantly better than other renal biomarkers, including plasma or urine NGAL or urine TIMP2-IGFBP7, in predicting progression to stage 3 AKI and need for RRT. Combining FST with individual biomarkers using logistic regression did not improve risk stratification significantly. When FST was assessed in patients with increased biomarker levels, the AUROC for progression to stage 3 improved to 0.90, and the AUROC for receipt of RRT improved to 0.92. Overall, in the setting of early AKI, FST performed better in predicting progressive AKI, need for RRT, and inpatient mortality than biochemical biomarkers.[21] A recent multicenter randomized controlled trial of 162 ICU patients with AKI of any stage (selected using a plasma NGAL greater than 150 ng/mL or fractional excretion of urea greater than 50%) with no immediate need for RRT had all patients undergo an FST.[22] Patients who failed to respond to the FST were randomized to early dialysis (within six hours) or standard care (dialysis when prompted by traditional indications, such as hyperkalemia or volume overload). Most patients were from a medical ICU with sepsis (58%) and requiring vasopressor support (78%). Of 44 patients who responded to the FST, only six patients (14%) required dialysis. In contrast, in patients who failed

to respond to the FST and were randomized to conventional management, 45 (75%) ultimately required dialysis. FST, therefore, appeared to be a good predictor of the need for dialysis. It also was a strong predictor of death. Among FST-responders, mortality was 34%, compared to 60% among FST non-responders. The FST was a more accurate predictor of mortality than Acute Physiology and Chronic Health Evaluation (APACHE) II or Sequential Organ Failure Assessment (SOFA) scores.[22]

Potential limitations for FST include: CKD, since studies have not included patients with a GFR less than 30 mL/min and performance in this scenario is unknown; hypoalbuminemia, since albumin is involved in the binding of furosemide and transport to the proximal convoluted tubule (some FST trials have excluded patients with albumin < 2 g/dL); and hypovolemia, since studies of FST have excluded these patients.

NGAL. In a study including 189 patients with AKI stage 3 secondary to moderate to severe community-acquired pneumonia, plasma NGAL was evaluated as a predictor of RRT, renal recovery, and in-hospital mortality. Those patients who required RRT and did not survive had a median plasma NGAL level between 370-588 ng/mL compared to 165-200 ng/mL for those who survived and did not require RRT. In addition, a median plasma NGAL level of 393 ng/mL had excellent specificity (90%) and positive predictive value (83%) for persistent need for RRT.[23] In another study of patients with AKI requiring RRT, the per-formance of urinary NGAL measured on days 1, 7, and 14 in combination with clinical variables, such as age and Charlson comorbidity index, showed that the rate of decline of NGAL at day 14 or a decline greater than 50% had an AUROC of 0.80 and AUROC of 0.90, respectively, of predicting renal recovery at day 60.[24]

CysC. In a cohort of 72 patients with established non-oliguric ATN, urine CysC > 1 g/mmol of creatinine had a sensitivity of 93% and specificity of 83% (AUROC 0.92) in predicting the need for RRT.[25] In contrast, serum CysC was not superior to serum creatinine in terms of short-term adverse outcomes, including RRT. However, the combination of serum creatinine and CysC seemed to add benefit for predicting adverse outcomes, including hospital mortality and dialysis in patients with AKI post-cardiac surgery.[26]

TIMP2 and IGTBP7. In a cohort of 719 critically ill patients, those with AKI and elevated urinary TIMP2-IGFBP7 of more than 0.3 $(ng/mL)^2/1,000$ were found to have an increased risk of ICU mortality or the need to initiate continuous RRT (CRRT) (adjusted hazard ratio [HR], 2.04) compared with AKI patients with TIMP2-IGFBP7 less than or equal to 0.3 $(ng/mL)^2/1,000$.[27] Using the KDIGO bundle, an intervention that consists of hemodynamic optimization, avoidance of nephrotoxic drugs, and prevention of hyperglycemia, could significantly lower the occurrence of moderate to severe AKI within the first 72 hours after cardiac surgery in high-risk patients defined by urinary TIMP2-IGFBP7 greater than 0.3 $(ng/mL)^2/1,000$ compared with controls (absolute risk reduction [ARR] 16.6%), but has no impact on the need for RRT at 60 or 90 days, ICU length of stay, or mortality at 60 or 90 days.[28] In a secondary analysis of a multinational prospective cohort of critically ill patients without AKI at enrollment, investigators found that elevated urinary TIMP2-IGFBP7 was associated with an increased risk of long-term adverse outcomes, including mortality and receipt of RRT at nine months. In addition, a TIMP2-IGFBP7 level greater than 2.0 $(ng/mL)^2/1,000$ was strongly associated with lack of renal recovery at 60 and 90 days and increased mortality.[21]

OTHER BIOMARKERS UNDER INVESTIGATION

C-C motif chemokine ligand 14 (CCL14) is a new biomarker that was developed to assess for persistent AKI (stage 2 or 3) or AKI that does not resolve for three or more days. In a multinational study including 364 patients with stage 2 and 3 AKI, the predictive ability of urinary CCL14 for persistent AKI or renal non-recovery lasting 72 hours or more was the highest (AUROC 0.83) when compared to other biomarkers, including plasma/urinary NGAL, urinary TIMP-2-IGFBP7, and plasma CysC.[29]

Urine kidney injury molecule-1 (KIM-1)[30] and urine L-type fatty acid binding protein (L-FABP)[31] also have been investigated extensively as early markers of AKI and as predictors of progression of AKI, need for RRT, and short-term mortality. Their AUROCs have ranged from 0.70 to 0.79, but with variable cutoffs, and performance has not been consistent across all types of AKI.

SUMMARY

AKI is a highly complex and continuous condition with multiple etiologies and potential mechanisms. As such, more than one renal biomarker may be needed to predict the onset of AKI accurately, progression to more severe stages, the need for RRT, and either persistent renal injury or renal recovery. Furthermore, the same biomarker may not be able to distinguish between all etiologies for AKI (e.g., sepsis, drug-induced, post-cardiac surgery, or hepatorenal). Currently, functional tests like the FST can predict progression to severe AKI, but reliable stress and

damage biomarkers still are needed to predict new onset AKI, renal recovery, or long-term need for RRT accurately. ■

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The list of references for this article is available online: https://bit.ly/3yNRnOe

ABSTRACT & COMMENTARY

Lung Protective Ventilation in ARDS: What Is the Best Strategy?

By Betty Tran, MD, MSc

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SYNOPSIS: Using newer methodology in network meta-analysis to compare various protective mechanical ventilation strategies, the authors concluded that a low tidal volume strategy combined with prone ventilation was associated with the greatest risk reduction in mortality for moderate to severe acute respiratory distress syndrome.

SOURCE: Sud S, Friedrich JO, Adhikari NKJ, et al. Comparative effectiveness of protective ventilation strategies for moderate and severe acute respiratory distress syndrome. A network meta-analysis. *Am J Respir Crit Care Med* 2021;202:1366-1377.

Current clinical guidelines recommend the use of low tidal volume (Vt), high positive end-expiratory pressure (PEEP), and prone ventilation in preventing ventilator-induced lung injury (VILI) in patients with acute respiratory distress syndrome (ARDS). However, few trials compare each of these interventions head-to-head, making it difficult to gauge their comparative effectiveness. Using current network meta-analysis methodology that incorporates not only statistical analyses but also certainty of evidence assessments, Sud et al conducted a network meta-analysis of 34 randomized controlled trials (RCTs) of adult ARDS patients to compare the relative effects of low Vt (< 8 mL/kg of ideal body weight), low Vt combined with high PEEP, venovenous extracorporeal membrane oxygenation (VV ECMO), high frequency oscillation (HFO), and prone ventilation with either low or high Vt on hospital mortality (if this was not available, mortality at the longest available duration of follow-up was used).

Using a frequentist random-effects network meta-analysis method, network risk ratios were calculated for each treatment strategy using low Vt as the standard comparator, given its wide acceptance as standard of care in ARDS.[1] A surface under the cumulative ranking curve (SUCRA) statistic (range 0% to 100%) was calculated, with higher values representing a higher likelihood that a therapy was among the best in the network meta-analysis. In addition, the Grading of Recommendations Assessment, Development and Education (GRADE) methodology was used to assess the certainty of evidence (moderate to high vs. low to very low).[2] Interventions then were classified by effectiveness (among the most effective, inferior to the most effective/superior to the least effective, and least effective) and certainty of evidence using high Vt as the referent least effective strategy and low Vt as the referent standard of care.

In the 34 RCTs analyzed, 9,085 ARDS patients had mortality data available. Median PaO_2/FiO_2 was 118 mmHg (interquartile range [IQR], 110-143), and median PEEP level was 12 cm H_2O (IQR, 10-13). A combination low Vt and prone strategy reduced mortality compared to low Vt alone (risk ratio [RR], 0.74; 95% confidence interval [CI], 0.60-0.92; high certainty) and when compared to HFO, a high Vt/prone combination, and high Vt strategies. VV ECMO reduced mortality compared to a high Vt or high Vt/prone strategy, but not compared with a low Vt (RR, 0.78; 95% CI, 0.58-1.05; very low certainty) or low Vt/prone strategy (RR, 0.95; 95% CI, 0.66-1.37; very low certainty). When the interventions were categorized as being among the best, intermediate, or worst based on certainty of evidence and SUCRA, a low-Vt/prone strategy was deemed among the most effective (SUCRA, 92%) for reducing ARDS mortality with high confidence. Although VV ECMO had a SUCRA value of 86%, the certainty of evidence was very low/low because of moderate risk of bias, imprecision, and intransitivity due to inclusion of more severely hypoxic patients. Low Vt/high PEEP and low Vt were ranked as being intermediately effective (i.e., not as effective as low Vt/prone, but better than high Vt) with moderate certainty of evidence.

■ COMMENTARY

This study had several strengths. The authors had a very specific analysis plan using state-of-the-art methodologies that considered not only statistical results, but also considered other factors (e.g., transitivity, imprecision, bias) that affect certainty of evidence and, thereby, the ability to make appropriate inferences about the best ventilation strategy. They also were meticulous in their classification of interventions, for example, distinguishing between trials with a low Vt vs. low VT/high PEEP strategy. They included a greater number of trials (and, therefore, participants) compared to prior analyses.

These findings do not necessarily contradict prior results from other meta-analyses, although the authors emphasized that their main recommendation (lowest mortality reduction seen in the low Vt/prone group) is distinct from another network meta-analysis, which concluded that both prone positioning and VV ECMO should be used in addition to a lung protective ventilation strategy.[3-5] This distinction was attributed to judicious application of GRADE to reveal much higher certainty of evidence supporting low Vt/prone than for VV ECMO rather than the use of SUCRA statistics alone. From a scientific perspective, it highlights and addresses concerns that analyses based solely on statistical methods can lead to errors in inference and, thus, validity.

Based on the conclusions from this study, a low Vt/prone strategy would be reasonable to use first, even in severe ARDS cases, given that proning can be performed in any intensive care unit (ICU) with proper training of staff. In contrast, VV ECMO requires high-risk transfer to one of few expert centers, is highly resource intensive, and comes with risk of serious complications, which are notable concerns in light of the low certainty of evidence. In cases where patients clinically deteriorate despite proning, VV ECMO could be considered for patients with severe ARDS. ■

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ABSTRACT & COMMENTARY

Dexmedetomidine and Temperature Elevation: Is the Link Important?

By Betty Tran, MD, MSc

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SYNOPSIS: In this post hoc analysis of the SPICE III trial, a greater percentage of patients receiving dexmedetomidine had temperatures greater than or equal to 38.3°C and 39.0°C compared to usual care. Although there was a significant dose response relationship between dexmedetomidine received and increase in temperature, there was no difference between groups in terms of paracetamol, antimicrobial, neuromuscular blocker, neuroleptic drug use, blood cultures performed, or initiation of renal replacement therapy.

SOURCE: Grayson KE, Bailey M, Balachandran M, et al. The effect of early sedation with dexmedetomidine on body temperature in critically ill patients. *Crit Care Med* 2021;49:1118-1128.

This was a post hoc analysis of the Sedation Practice in Intensive Care Evaluation (SPICE) III trial, which enrolled 4,000 mechanically ventilated patients in eight countries to receive solely dexmedetomidine or usual care (propofol, midazolam, or other sedatives).[1] Patients enrolled in SPICE III were expected to remain on ventilator support beyond the calendar day following randomization, were enrolled within 12 hours of intubation, and required immediate sedatives for comfort and safety; notably, primary brain or spinal cord injury patients were excluded. Randomization

was 1:1 and stratified by center and according to the presence/absence of sepsis. Sedation was targeted to a Richmond Agitation Sedation Score (RASS) of -2 (light sedation) to +1 (restless). If target sedation was not achieved with maximum dose dexmedetomidine, propofol was added at the lowest dose to reach the RASS goal. All sedatives were administered open label.

For this study, only 708 patients (17.7%) from four intensive care units (ICUs) contributed data for analysis (50.1% randomized to dexmedetomidine). The primary outcome was mean body temperature from randomization to day 5, ICU discharge, or death (temperature was measured every six hours). Secondary outcomes were measured within the same time frame and included highest daily body temperature and percentage of patients in each group with mild (> 38.3ºC) and severe (> 39ºC) body temperature elevations. Data were collected on the use of paracetamol, intravenous (IV) antibiotics, neuromuscular blockers, neuroleptic drugs, renal replacement therapy, and blood cultures drawn. A priori subgroups to evaluate for effect modification included below/above the median age of 63.7 years in SPICE III, presence/absence of sepsis, and weight less/more than 120 kg.

Mean daily temperature was not significantly different between the dexmedetomidine and usual care groups (absolute difference, 0.06ºC; 95% confidence interval [CI], -0.03ºC to 0.15ºC; $P = 0.16$). However, more patients receiving dexmedetomidine vs. usual care recorded a mild temperature elevation > 38.3ºC (absolute difference, 10.6%; 95% CI, 3.5-17.8%; $P = 0.004$) and severe temperature elevation > 39ºC (absolute difference, 6.9%; 95% CI, 1.5-12.3%; $P = 0.013$). These between-group differences equate to a number needed to harm (NNH) to cause a temperature > 38.3ºC and > 39ºC of 9.4 and 14.5, respectively.

When dexmedetomidine usage was analyzed as a continuous variable, for every additional 1 µg/kg/hour, temperature increased by 0.30ºC + 0.08ºC ($P < 0.0002$). The daily and total doses of paracetamol, number of antibiotic days, use of neuromuscular blockers and neuroleptic agents, number of blood cultures collected, and use renal replacement therapy were similar between groups. Patients receiving dexmedetomidine who were greater than 120 kg were more likely to have elevated temperatures compared to patients with lower body weight ($P = 0.02$), despite the dose calculation being capped at 100 kg. There was no significant heterogeneity of dexmedetomidine effect in the other subgroups of age and sepsis.

■ COMMENTARY

Dexmedetomidine has generated recent interest as a primary sedative in the ICU, given its ability to induce sedation while maintaining respiratory drive and some arousability. Its potential benefits include a reduction in ICU length of stay, delirium, duration of mechanical ventilation, and, possibly, mortality.[2-5] Commonly reported side effects include bradycardia and hypotension. There are case series documenting hyperthermia, some of which have required other interventions, such as dantrolene and initiation of renal replacement therapy, as usual cooling methods were ineffective.[6-7]

Although this study did report that a greater percentage of patients had elevations in temperature associated with dexmedetomidine, this was not the primary outcome. In addition, although this was the first randomized controlled data reporting an association between dexmedetomidine and temperature elevation, it was a post hoc analysis, and as such, all differences between the two groups studied should not be considered definitive given underlying multiple statistical comparisons.

Nevertheless, the results do support the observation that hyperthermia can be a side effect of dexmedetomidine, which was reported in prior case series. However, whether this side effect results in significant untoward complications is unclear. There was no increase in the number of blood cultures performed or number of days of antibiotic and/or paracetamol use in patients assigned to dexmedetomidine. However, given that this was an open-label trial, it is possible that clinicians were aware that dexmedetomidine may be responsible for the temperature elevations observed. Indeed, this study highlights an important take-home message for the ICU practitioner: In patients receiving mechanical ventilation, dexmedetomidine should be considered as a potential cause of unexplained temperature elevations. ■

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CME/CE QUESTIONS

1. **The utility of the furosemide stress test is in:**
   a. recognizing early acute kidney injury (AKI).
   b. predicting renal recovery.
   c. reducing the severity of established AKI stage 3.
   d. predicting the progression of early AKI.

2. **Which of the following is true regarding renal biomarkers?**
   a. CCL14 is a marker for early recognition of AKI.
   b. Serum cystatin C is a strong predictor of AKI requiring renal replacement therapy (RRT).
   c. Patients with AKI and plasma neutrophil glatinase-associated lipocalin (NGAL) greater than 370 ng/mL have an increased risk of requiring RRT and mortality.
   d. Use of a Kidney Disease: Improving Global Outcomes (KDIGO) bundle in combination with urine tissue inhibitor of metalloproteinases-2/insulin-like growth factor binding protein 7 (TIMP2-IGFBP7) improves mortality and reduces need for AKI requiring RRT.

3. **In the network meta-analysis by Sud et al, which intervention was associated with the largest reduction in mortality among patients with moderate to severe acute respiratory distress syndrome (ARDS)?**
   a. Venovenous extracorporeal membrane oxygenation
   b. Low tidal volume ventilation
   c. Low tidal volume combined with prone ventilation
   d. Low tidal volume combined with high positive end-expiratory pressure ventilation

4. **Which of the following was a finding in the post hoc analysis of the SPICE III trial that compared mechanically ventilated patients receiving dexmedetomidine to usual care?**
   a. Patients receiving dexmedetomidine had a higher mean daily body temperature.
   b. A larger proportion of patients receiving dexmedetomidine had mild or severe elevations in body temperature.
   c. Patient receiving dexmedetomidine had more blood cultures drawn.
   d. Dexmedetomidine's temperature effect was more pronounced in younger and septic patients.

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.

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