Perioperative ACE Inhibitors/Protective Ventilation Strategies

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Case study: male patient in preoperative area 7:00 AM for laparoscopic inguinal hernia repair; hypertension well controlled; medications include losartan, lisinopril, hydrochlorothiazide, amlodipine, metoprolol, and others; patient took all medications morning of surgery; preoperative blood pressure 130/65 mm Hg; patient taken to operating room and monitors attached; induction performed and patient intubated; blood pressure 70/30 mm Hg, and 80/45 mm Hg on second cycle; blood pressure falling; phenylephrine given; blood pressure increased, then decreased again

“Triple hit” factors contributing to hypotension after induction: hypovolemia, pharmacologic manipulation of renin-angiotensin system, and half-life and duration of action of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)

Hypovolemia: causes exaggerated responses to medications that decrease systemic vascular resistance (eg, propofol); nothing-by-mouth status can contribute to hypovolemia; patients with hypertension chronically hypovolemic because of loss of salt and water; kidneys interpret high pressure as overload of volume and eliminate water; administration of diuretics contributes to hypovolemia

Renin-angiotensin system: renin released from kidneys in response to hypotension, hyponatremia, or stimulation of sympathetic nervous system; bradykinin (vasodilatory peptide) is key to pathway; aldosterone and antidiuretic hormone (ADH) increase reabsorption of free water; angiotensin II targeted by ARBs; angiotensin II works in combination with renin, bradykinin, aldosterone, and ADH to maintain extracellular fluid volume and blood pressure; decreased blood pressure, sodium levels, and blood volume stimulate release of renin; renin converts circulating angiotensin into angiotensin II; angiotensin II receptors increase extracellular fluid volume by reabsorption of salt and water; angiotensin II increases total peripheral resistance; net effect of process increased blood pressure and blood volume

ACE inhibitors and ARBs: ACE inhibitors block conversion of angiotensin I to angiotensin II (decreasing vasoconstriction and blood pressure) and prevent breakdown of bradykinin; bradykinin causes vasoconstriction and decrease in blood pressure; ARBs prevent angiotensin II from binding to receptors; net effect of ACE inhibitors and ARBs increased bradykinin, decreased vasoconstriction, decreased release of aldosterone and vasopressin; they manipulate body’s normal responses to hypovolemia; reset of arterial baroreceptors attenuates response of heart rate to hypovolemia; response to exogenous catecholamines decreased; ACE inhibitors and ARBs create sympatholytic state

Pharmacology of ACE inhibitors and ARBs: degree of hypotension depends on duration of action of drug; half-lives vary from 1 hr to 38 hr, but duration of action much longer; variable durations of action present difficulties for stopping medications before surgery

Stopping vs continuing medications before surgery: discontinuing ACE inhibitors or ARBs potentially prevents refractory hypotension and cancellation of procedure, but it may also create hypertension and remove protective benefits during perioperative period; continuing medications decreases confusion and preserves protective effects but contributes to risk for refractory hypotension

Randomized controlled trials: 3 studies demonstrated that withdrawal of ARB therapy may cause hypotension, but studies inadequately powered and failed to address outcomes; fourth study, Twersky et al (2014), assessed effect of withdrawal on development of hypertension in ambulatory surgical patients; found statistically nonsignificant increase in hypertension in patients who did not take medications day of surgery; studies reached conflicting conclusions

Observational propensity score-matched studies: may be grouped into categories of cardiac, vascular, and noncardiac surgery; in cardiac and vascular groups, increased incidence of hypotension occurred regardless of continuation or discontinuation; statistically significant increase in mortality at 30 days and development of acute kidney injury in cardiac and vascular patients who continued medications; in 2 studies, discontinuation of medications for cardiac surgical patients recommended; in noncardiac patients, hypotension demonstrated if ARB associated with diuretics, but no difference in mortality at 30 days or cardiac morbidity; Nielsen et al (2014) found increased incidence of hypotension and acute kidney injury in orthopedic patients who continued medications

Recommendations: no consensus on stopping vs continuing medications in literature; no clear consensus for recommendations among medical societies; variation in practice across facilities; speaker suggests that practice of stopping medications day before surgery does not make sense; speaker recommends continuing to evaluate literature (studies underway) for procedure-specific studies and for risk stratification of patients; optimal timing for discontinuation of medications unclear; individualize decision for each patient

First-line treatments for refractory hypotension: preoperative fluids first-line treatment; hypertension leads to hypovolemia, particularly in patients taking diuretic, ACE inhibitor, and ARB; first-line medications ephedrine and phenylephrine, but larger than usual dosages required; study indicated triple usual dosage

Educational Objectives

The goals of this program are to improve the management of refractory postinduction hypotension and to optimize strategies for ventilation. After hearing and assimilating this program, the clinician will be better able to:

1. Describe the mechanisms and pathophysiology of postinduction hypotension.
2. Cite current literature addressing perioperative discontinuation of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.
3. Outline a treatment plan for intraoperative management of refractory hypotension.
4. Explain the rationale for the use of protective ventilation strategies.
5. Apply appropriate elements of protective strategies to intraoperative ventilator management.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose.
of ephedrine required; consider early use of glycopyrrolate to increase heart rate and augment cardiac output in patients with low stroke volume

Second-line agents: norepinephrine helps replace decreased level of circulating catecholamines; vasopressin considered first-line agent by speaker; vasoconstriction mediated by V1 and V2 receptors not attenuated by angiotensin receptor blockade; all these drugs have short half-lives, so infusions required

Methylene blue: third-line agent; decreases cyclic guanosine monophosphate, which leads to decrease of smooth muscle relaxation; dosage 1 mg/kg to 2 mg/kg intravenously; duration of effect ≤10 min (in literature, 40 min); may precipitate serotonin syndrome in patients taking selective serotonin reuptake inhibitors

Suggested Reading


Protective Ventilation Strategies: ICU, Intraoperative, or Both?

Peter K. Schoenwald, MD, Associate Professor of Anesthesiology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University; Associate Program Director, Anesthesiology Education, Cleveland Clinic, Cleveland; Staff Anesthesiologist, Department of General Anesthesia, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH

Roupie et al (1995): sought to determine optimal tidal volume and method of titration; animal studies had showed negative outcomes if alveoli overdistended (mechanism unclear); overdistention in animals led to condition resembling acute respiratory distress syndrome (ARDS); mortality rate relatively high in patients with ARDS; identified 42 patients with pulmonary injury, based on FiO₂ ≥0.5; separated patients into group meeting criteria for ARDS and group that did not; determined static pressure-volume curve every 2 days; noted 2 inflection points; lower inflection point indicates opening of last few alveoli; upper inflection point indicates over-extension; patients initially ventilated with positive end-expiratory pressure (PEEP) at lower inflection point, and tidal volume 10 mL/kg; in all patients with ARDS, upper inflection point observed; in patients not meeting criteria for ARDS, only one showed upper inflection point below maximum tidal volume of 1600 mL; in patients with ARDS, 80% required reduction in tidal volume to remain below upper inflection point; points on curve above and below inflection points likely to lead to lung injury

Amato et al (1998): patients with ARDS assigned to conventional ventilation strategy, defined as tidal volume 12 mL/kg, minimal PEEP, and normal carbon dioxide, or to protective strategy of tidal volume <6 mL/kg, PEEP above lower inflection point, permissive hypercapnia, and driving pressure limited to <20 cm H₂O above PEEP; observed improved survival at 28 days, higher rate of weaning, and lower rate of barotrauma in group with protective strategy; not associated with higher survival rate before discharge

Stewart et al (1998): patients at high risk for ARDS assigned to conventional strategy of tidal volume 10 mL/kg to 15 mL/kg and peak inspiratory pressure (PIP) ≤50 cm H₂O, or to limited protective strategy of tidal volume <8 mL/kg, PIP <30 cm H₂O, and pressure- or volume-limited mode; no statistical difference in mortality between groups; hypercapnia more common in limited group, no differences in episodes of organ failure, but more dialysis in limited group; concluded protective strategy does not reduce mortality and may increase morbidity in patients at high risk

Acute Respiratory Distress Syndrome Network study (2000): multicenter trial of patients with ARDS; in control group, tidal volume 12 mL/kg and plateau pressure ≤50 cm H₂O; study (protective) group tidal volume 6 mL/kg and plateau pressure <30 cm H₂O; clinically significant lower mortality and less ventilator days seen in study group; ended study early; concluded that lower tidal volumes associated with significantly lower mortality and with fewer ventilator days in patients with lung injury

Protective strategy in ARDS: minimize shear stress by lower inflection point (atelectrauma) caused by cyclic opening, recruitment, and derecruitment of alveoli; optimize PEEP, PEEP higher than historically used; minimize volume overdistention; tidal volumes lower than historically used; role of recruitment maneuvers unclear; numerous studies have demonstrated better outcomes in patients in intensive care unit (ICU) with ARDS using lower tidal volumes and lower PEEP

Difficulties in applying strategy to intraoperative ventilation: studies conflicting; definitions of high, normal, and low tidal volumes and PEEP vary; to speaker, conclusions “taken out of context” if applied to operating room (OR); meta-analyses of very small studies prone to small-volume errors; necessary to use consistent definition of desired postoperative outcomes across studies before translating into clinical practice

Factors altering low tidal volume ventilation intraoperatively: laparoscopic surgery, steep Trendelenburg position, morbid obesity, restrictive lung disease, length of surgery, hypoxemia, hypercarbia, and acidosis; ventilators in OR vary in capabilities; defined outcome end points required; OR environment not static; patients exposed to varying surgical conditions

Blum et al (2011): assessed intraoperative ventilation of patients with lung injury; concluded anesthesiologists not managing ventilation according to ICU parameters

Serpa Neto et al (2012): performed meta-analysis to assess outcomes of protective ventilation strategies on patients without ARDS; concluded protective ventilation with lower tidal volumes associated with better clinical outcomes in these patients

Severgini et al (2013): divided 56 patients undergoing open abdominal surgery into standard group with tidal volume 9 mL/kg with no PEEP, and protective group with tidal volume 7 mL/kg, PEEP 10 cm H₂O, and recruitment maneuvers; concluded intraoperative protective ventilation led to better pulmonary function; unclear whether improvement because of lower tidal volume, permissive hypercapnia, and driving pressure limited to <20 cm H₂O above PEEP; observed improved survival at 28 days, higher rate of weaning, and lower rate of barotrauma in group with protective strategy; not associated with higher survival rate before discharge

Treschan et al (2012): included patients undergoing upper abdominal surgery; high tidal volume group 12 mL/kg, and low tidal volume group 6 mL/kg; PEEP used in both groups, and recruitment not used in either; found no benefit for low tidal volumes

Futier et al (2013): evaluated 400 at-risk patients undergoing major abdominal surgery; good separation between tidal volumes in standard and protective groups; no PEEP or recruitment in one group and PEEP and recruitment every 30 min in other group; assessed pulmonary and extrapulmonary complications that occurred within 7 days; fewer complications and shorter hospital stays in protective group

Goldenberg et al (2014): critique and commentary article; important to understand that critical care and operative populations different; protective ventilation may be beneficial if both low tidal
volumes and recruitment strategies utilized; parameters in Futier et al not limited to low tidal volume; size of effect (60% reduction) statistically unrealistically high; groups may not have been balanced at baseline; caution advised

**Levin et al (2014):** retrospective study of almost 30,000 patients found low intraoperative tidal volume with minimal PEEP associated with increased risk of mortality at 30 days; unclear whether related to tidal volume or PEEP

**Serpa Neto et al (2015):** meta-analysis of 15 trials sought to evaluate associations between tidal volume and PEEP with postoperative pulmonary complications; groups within analysis heterogeneous in terms of levels of PEEP used; significantly fewer complications in protective ventilation group; difference between low tidal volume/high PEEP and low tidal volume/low PEEP not clinically significant; concluded that beneficial effects of low intraoperative tidal volumes supported, but further trials needed to define role of higher intraoperative PEEP for abdominal surgery

**Contextual concerns:** results from studies taken out of context and applied elsewhere; studies use varying definitions of high and low tidal volume and PEEP; PEEP and recruitment procedures must be considered in addition to tidal volume

**Speaker's suggestions:** utilize moderate multiparameter approach of tidal volume 7 mL/kg to 8 mL/kg and PEEP 8 cm H2O to 10 cm H2O; maintain plateau pressure <30 cm H2O when possible; clinical conditions may require alteration of parameters

**Questions and answers:** changing inspiratory to expiratory ratios — has been mentioned in some studies, but not focus of studies; FiO2, oxygen toxicity, and rapid atelectasis — atelectasis may occur quickly, but not quickly enough to create major concern; oxygen 80% to 90% toxic over long term, and debated whether oxygen 50% may be toxic in short term; high oxygen concentration creates safety margin in some patient populations (eg, obese patients); individualize treatment plan; preferred FiO2 for routine cases — speaker used 0.5 in past but currently prefers ≤0.4; existence of studies showing worse outcomes with protective ventilation strategies — there is one, but again note that definitions of lung protective strategy vary

**Suggested Reading**


**Acknowledgments**

Dr. Kolarczyk spoke at the 29th Annual Carolina Refresher Course: *Update in Anesthesiology, Pain, and Critical Care Medicine*, presented by the University of North Carolina at Chapel Hill School of Medicine and the Mountain Area Health Education Center and held June 22-25, 2016, on Kiawah Island, SC. For information on upcoming CME meetings from the University of North Carolina at Chapel Hill School of Medicine, please visit med.unc.edu. For information on upcoming CME meetings from the Mountain Area Health Education Center, please visit mahec.net. Dr. Schoenwald spoke at the Survey of Current Issues in Surgical Anesthesia, presented by the Cleveland Clinic Anesthesiology Institute, and held November 30 to December 4, 2014, in Naples, FL. For information on upcoming CME meetings from the Cleveland Clinic Anesthesiology Institute, please visit ccfcme.org/GoSurgAnes. The Audio Digest Foundation thanks the speakers and the sponsors for their cooperation in the production of this program.

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**Estimated time to complete the educational process:**

**Review Educational Objectives on page 1**

Take pretest 5 minutes

Listen to audio program 10 minutes

Review written summary and suggested readings 35 minutes

Take posttest 10 minutes
1. Which of the following triggers the release of renin from the kidneys?
   (A) Hypertension  (C) Stimulation of the sympathetic nervous system**
   (B) Hypernatremia  (D) Stimulation of the parasympathetic nervous system

2. Which of the following is an effect of bradykinin?
   (A) Increased reabsorption of free water
   (B) Vasodilation**
   (C) Stimulating conversion of angiotensin I to angiotensin II
   (D) Preventing angiotensin II from binding to receptors

3. Which of the following is one of the net effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)?
   (A) Increased bradykinin**
   (B) Increased vasoconstriction
   (C) Increased aldosterone release
   (D) Increased vasopressin release

4. Which of the following was a finding of observational propensity score-matched studies evaluating perioperative discontinuation of ACE inhibitors and ARBs?
   (A) Increased incidence of hypotension in cardiac patients who continued or discontinued medications, compared to patients not taking medication**
   (B) Decreased incidence of acute kidney injury in vascular patients who continued medications
   (C) Decreased mortality at 30 days for cardiac patients who continued medications
   (D) Increased mortality at 30 days for noncardiac patients who continued medications

5. Which of the following are considered first-line treatments for refractory hypotension?
   1. Norepinephrine
   2. Phenylephrine
   3. Ephedrine
   4. Preoperative fluids
   5. Methylene blue
   (A) 1,2  (B) 3,4  (C) 2,3,4**  (D) 1,3,5

6. All the following statements are accurate about a study by Roupie et al (1995) examining static pressure-volume curves in ventilated patients, EXCEPT:
   (A) The upper inflection point of the curve corresponded with overextension of lungs and alveoli
   (B) Upper inflection points were observed in all patients with acute respiratory distress syndrome (ARDS)
   (C) Upper inflection points were observed in half the patients who did not meet the criteria for ARDS**
   (D) 80% of patients with ARDS required reductions in tidal volume to remain below the upper inflection point

7. In a study by Amato et al (1998) comparing a conventional ventilation strategy with a protective strategy, all the following were observed for the protective group, EXCEPT:
   (A) Improved survival at 28 days
   (B) Improved survival before discharge**
   (C) Higher rates of weaning
   (D) Lower rates of barotrauma

8. In a study by Stewart et al (1998), which of the following characterizes the group receiving a limited protective ventilation strategy compared with the group receiving a conventional strategy?
   (A) Increased mortality
   (B) Increased incidence of hyperventilation**
   (C) Decreased episodes of organ failure
   (D) Decreased requirement for dialysis

9. The authors of a study conducted by the Acute Respiratory Distress Syndrome Network (2000) found that lower tidal volumes were associated with _______ mortality and _______ ventilator days in patients with lung injury.
   (A) Higher; more  (B) Higher; fewer  (C) Lower; more  (D) Lower; fewer**

10. A protective ventilation strategy for patients with ARDS includes use of _______ positive end-expiratory pressure than traditionally used and _______ tidal volumes than traditionally used.
    (A) Higher; higher  (B) Higher; lower**  (C) Lower; higher  (D) Lower; lower

Attention, CME/CE Participants
The cutoff date for logging 2016 credits is December 31, 2016. Test forms received after that date will be accrued to 2017.

Answers to Audio Digest Anesthesiology Volume 58, Issue 39: 1-C, 2-B, 3-B, 4-C, 5-A, 6-C, 7-C, 8-D, 9-B, 10-D