MICU HANDBOOK

Contents

Curriculum on Critical Care Medicine (MICU) West Virginia University Internal Medicine Residency Program

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West Virginia University Internal Medicine Residency Program

Director of Rotation

John E. Parker, MD, Section Chief, Pulmonary and Critical Care Medicine

Kashif Hussain, MD, Medical Director, Intensive Care Unit

Maximum Number of Rotators per month

6-7 Housestaff, 1-2 Sub-interns

Educational Purpose and Goals

The critical care rotation exposes residents to patients with a broad variety of unstable, life threatening medical illnesses. Residents will learn the basic tenets of stabilization of critically ill patients, and understand the differential diagnosis and appropriate diagnostic work ups of such patients. They will function within multidisciplinary teams to provide care that is timely, appropriate and takes into account patient or family preferences.

Principle Teaching Methods

A. Supervised direct patient care activities: Resident teams participate in daily management and teaching attending rounds with their supervising attending. Residents assume primary care for the management and coordination of care for their patients, including performance of any necessary procedures.
B. Didactics:
-Pulmonary Case Conference-every Thursday from 4 pm to 5 pm
-Critical Care Medicine Journal Club- usually 3rd or 4th Tuesday of the month from 11:30 am to 1 pm

C. Assigned reading: Residents are expected to complete directed reading based upon their patient census.

D. Morbidity and Mortality Conference: These occur on monthly basis to review cases from the critical care unit.

Educational Content

A. Mix of disease: Patients on the Critical Care Service may have a variety of critical illnesses. Among these are: respiratory failure, ARDS, medical neurologic emergencies, infectious diseases, metabolic processes such as diabetic ketoacidosis, hypertensive emergencies, circulatory shock, drug over dose, septic shock and acute renal failure.

B. Patient Characteristics: Patients admitted to Ruby Memorial Hospital medical intensive care units are drawn from the general population of Morgantown area, as well as transfers from across the state of WV, Southwestern PA, Western MD and Southeastern OH. Patients requiring transfer to the MICU from the General Medical teams, Hem/Onc team and BMT services will also make up some of the patient population. In addition patients may be drawn from on-call responsibilities of residents; continuity clinics of residents or attending physicians; consults from other hospital physicians; or transfers from Healthsouth Rehabilitation Hospital.

C. Learning Venues:

a. Facility: The critical care rotation occurs at Ruby Memorial Hospital. Residents care for patients admitted to their service in the Medical Intensive Care Unit (MICU). The Health Sciences Center contains a full service medical library and computer facilities with Internet access for resident use. Each unit has on-line access to digitized imagery (PACS) of CT scans, MRI, MRA, PET/CT and plain films.

b. Procedures: Residents have the opportunity to perform a variety of procedures on patients under their care, including: central venous lines, Swan Ganz catheterization, temporary transvenous pacemaker placement, arterial lines, nasogastric tube insertion, intubation of the respiratory tract, paracentesis, thoracentesis, lumbar puncture, and arthrocentesis. Residents also have the opportunity to interpret all imaging studies and laboratory tests ordered on their patients. Radiology images are easily accessible from the MICU through PACS. Residents will also utilize standard ACLS protocols in the management of patients as needed. **Please remember the procedures have to be supervised by the faculty or fellows.**

c. Ancillary Services: During this rotation, residents interact wit subspecialists from a variety of disciplines; fellows in hematology/oncology, pulmonary and critical care medicine, nephrology; respiratory therapists; clinical pharmacists; residents from other disciplines who serve either as consultants (eg, surgery) or as junior residents (e.g. emergency medicine, family medicine, anesthesia.); case managers; and nursing personnel.

d. Structure of the Rotation

i. Teams: One team functions within the medical intensive care unit. Each team consists of a managing attending, a Pulmonary/Critical Care Medicine fellow, 4 senior residents, 2-3 interns and medical students (primarily 4th year sub-interns). In addition, there are designated senior residents per month who are the ICU night float resident and help the on-call resident with the admissions and existing patients, on both the MICU and the CCU.

ii. Duty Hours: All residents schedules are structured to limit duty hours to no greater than 80 hours per week, when averaged over four weeks. On average, a resident is scheduled for 72 hours per week during this rotation. All internal medicine residents are relieved from their continuity clinics during this month.

iii. Call: Interns are on-call for admission every other day, during the daytime from 7 am to 5 pm and are expected to the MICU admission beeper and MICU phone (75454) during this time. Senior residents are on-call every 4th day, from 5 pm to 7 am. On-call senior resident is expected to come in at 4 pm to take part in the evening round and take check-out from the dayteam. Pulmonary and Critical Care Medicine fellows are assigned out-of-house call daily and will come in when called to help with the management or procedure for new admission and other existing ICU patients.

iv. Rounds: Management and teaching attending rounds occur daily with all members of the team present. Start times are pre-arranged between attendings and residents usually every morning. Discussion and care is provided at the bedside. Radiographic images may also be viewed electronically during management rounds. MICU daily rounds are multidisciplinary and besides physicians, a pharmacist, dietician, respiratory therapist and bedside nurse are team members. They should be involved in each care discussion.

v. Clinics: Senior residents continue to participate in continuity clinics one half day per week, unless such participation would conflict with post call duty hour restrictions. Junior residents have their continuity clinic cancelled while on this rotation.

vi. Lectures: All residents continue to participate in residency-wide conferences as noted previously, including the Core Noon conference series.

III. Consultation

The MICU Team provides "vent" consults on Med-C-CCU patients. The SICU or CTU team may request consultation as well.

IV. ICU Protocols & Guidelines

They will be given to you in the beginning of each month. If not provided, please ask faculty or fellow to get you a copy.

V. Pharmaceutical Drug Studies

There are many "drug trials" (new experiment) going on in the ICU. You are encouraged to learn and participate in them.

VI. Principle Ancillary Educational Materials

A. Residents are assigned targeted reading in primary literature sources by Teaching Attending physicians throughout the rotation.

B. Full service 24-hour libraries are present at the Health Sciences Center of the Robert C. Byrd Health Sciences Center with onsite medical librarians. Web-based searchable medical databases are available through those libraries, and standard medical journals are available in both print and electronic formats. In addition, all residents have 24-hour accessibility to the extensive online West Virginia University electronic library, including databases and electronic journals.

C. Computer based resources are available at the hospital to facilitate patient care, education and communication. The following are made available:

1. Up-To-Date Online
2. Drug information resources including side effects and drug-drug interactions
3. Electronic Medical Record (Citrix)
4. Radiology results retrieval (PACS)
5. E-mail service via the internet
6. Electronic textbooks of medicine

D. In the residency office and hospital libraries, a number of videotapes and audiotapes are available including:

1. MKSAP booklets
2. Assorted procedures videotapes
3. MedStudy materials

E. The primary textbook is *Intensive Care Medicine*, Richard S. Irwin, M.D. (Editor) and James M. Rippe, M.D. (Editor)

VII. Methods of Evaluation

A. Resident Performance

i. Faculty complete web-based (E*Value) electronic resident evaluation forms provided by the Internal Medicine Residency office. The evaluation is competency-based. The evaluation is shared with the resident, is available for on-line review by the resident at their convenience, and is internally reviewed by the residency office. The evaluation is part of the resident file and is incorporated into the semiannual performance review for directed resident feedback.

ii. Residents electronically record completed procedures on the E*Value system. The supervising physician verifies the resident understands the procedure's indications, contraindications, complications and interpretation.

iii. Chart audits are conducted on at least one resident-generated document each rotation, with specific feedback given to the resident on data-gathering and documentation skills.

B. Program and Faculty Performance

i. Using the E*value system upon completion of the rotation, residents complete a service evaluation commenting on the faculty, facilities and service experience. Evaluations are reviewed by the program and attending faculty physicians receive anonymous annual copies of aggregate completed evaluations. Collective evaluations serve as a tool to assess faculty development needs. The Education Committee reviews results annually.

VIII. Institutional Resources

A. Strengths: Ruby Memorial Hospital serves as a tertiary care and Level One trauma center for outlying communities. This provides a breadth and depth of patient care, particularly in the intensive care units, which is not seen in smaller systems. Critical care attendings perform dedicated rounds with a multidisciplinary team

B. Weaknesses: There is no active renal, liver, pulmonary or cardiac transplant program. Adolescents, including young adults (i.e. early 20's) with chronic diseases, are frequently admitted to the Pediatric Intensive Care service. This service is separately staffed and located, and does not interact with the adult ICU program.

VII. Rotation Specific Competency Objectives

A. Patient Care

i. History taking. Residents at all levels of training will collect a thorough history, by soliciting patient information, and consulting other sources of primary data in a logical and organized fashion. History taking will be hypothesis driven. Interviewing will adapt to the time available and instability of the patient, use appropriate nonverbal techniques, and demonstrate consideration for the patient and family. The resident will inquire about the emotional aspects of the patient's or family's experience while demonstrating flexibility based on patient need. Residents will recognize verbal and nonverbal cues from the patient. Cues will be followed in an organized directed logical fashion with a complete exploration of symptoms.

ii. Physical Exam. Residents at all levels of training will perform a comprehensive physical examination describing the physiological and anatomical basis for normal and abnormal findings. PGY2 and 3 residents will demonstrate knowledge of maneuvers that can elicit findings not otherwise present, and routinely adapt the physical exam for patients with diminished levels of consciousness or cooperativeness.

iii. Charting. Residents at all levels of training will record data in a legible, thorough, systematic manner. Please use ICU computerized forms for daily notes, admissions and procedures.

iv. Procedures.

1. PGY-1 and PGY-2 residents will demonstrate knowledge of: procedural indications, contraindications, necessary equipment, specimen handling, patient after-care, and risk and discomfort minimization. They will participate in informed consent and assist

patients with decision making. They will correctly identify the meaning of test results. PGY1 residents will initially observe and then perform procedures prior to the completion of the first training year.
2. PGY-3 residents will demonstrate extensive knowledge and facility in the performance of procedures while minimizing risk and discomfort to patients. They will assist their junior peers in skill acquisition.

v. Medical Decision Making, Clinical Judgment, and Management Plans. All residents will demonstrate improving skills in assimilating information that they have gathered from the history and physical exam.

1. PGY-1 residents will be able to identify patients' problems and develop a prioritized differential diagnosis. Abnormal findings will be interrelated with altered physiology. They will understand their limitation of knowledge and seek the advice of more advanced clinicians. PGY-1 residents will begin to develop therapeutic plans that are evidence or consensus based. Residents will establish an orderly succession of testing based on their history and exam findings. Specific organ dysfunction will be anticipated based on known side effects of therapy. Additionally, residents will understand the correct administration of drugs, describe drug-drug interactions, and be familiar with expected outcomes.

2. PGY-2 residents will also regularly integrate medical facts and clinical data while weighing alternatives and keeping in mind patient preference. They will regularly incorporate consideration of risks and benefits when considering testing and therapies. They will present up-to-date scientific evidence to support their hypotheses. They will consistently monitor and follow-up patients appropriately. They will develop plans to avoid or delay known treatment complications and be able to identify when illness has reached a point where treatment no longer contributes to improved quality of life.

3. PGY-3 residents will demonstrate the above and in addition, will demonstrate appropriate reasoning in ambiguous situations, while continuing to seek clarity. Residents at this level of training will not overly rely on tests and procedures. PGY-3 residents will continuously revise assessments in the face of new data.

vi. Patient counseling

1. PGY-1 residents will be able to describe the rationale for a chosen therapy and will be able to describe medication side effects in lay terms. They will assess patient/family understanding and provide more information when necessary. Residents will demonstrate the ability to be a patient advocate.

2. PGY-2 residents, in addition to the above, will be able to explain the pros and cons of competing therapeutic interventions. PGY-2 residents will be expected to counsel patients regarding adverse habits, and educate patients and families for enhanced compliance. They will be able to effectively communicate with critically ill patients and engage patients and families in end-of- life discussions.

3. PGY-3 residents, in addition to the above, will effectively communicate with patients making life-style modifications.

B. Medical Knowledge.

1. The resident will acquire knowledge, problem solving ability, practical skills and an attitude applicable the care of critically ill patients.
2. The resident will become familiar with appropriate diagnostic, therapeutic, and hemodynamic monitoring techniques.
3. The resident will develop the ability to respond rapidly and appropriately to life-threatening problems and grow to become an effective judge of the priorities of resuscitation.
4. The resident will learn to act appropriately as a member or leader of a therapeutic team which includes nurses, pharmacists, and ethicists.
5. The resident will learn to appreciate and hopefully modify the stresses which the Intensive Care environment places upon the patient, their relatives, members of the ICU staff, and themselves.
6. The resident will begin to understand how to use health care financial resources effectively and prevent the Critical Care Unit from simply becoming an "Expensive Care Unit".
7. The resident will continue to develop the habit of self assessment and realize the limitations in the practice of this specialty.
    a. PGY-1 residents will consistently apply current concepts in the basic sciences to clinical problem solving. They will use information from the literature and other sources including electronic databases. PGY-1 residents will demonstrate satisfactory knowledge of common medical conditions, sufficient to manage urgent complaints with supervision. Residents must exhibit sufficient content knowledge of common conditions to provide care with minimal supervision by

completion of the PGY-1 year.

b. PGY-2 residents will demonstrate a progression in knowledge and analytical thinking in order to develop well-formulated differential diagnoses for multi-problem patients. They will also demonstrate socio-behavioral knowledge.

c. PGY-3 residents in addition to the above will demonstrate appropriate habits to stay current with new medical knowledge, and will exhibit knowledge of effective teaching methods.

C. Interpersonal and Communication Skills.

1. PGY-1 residents will develop and refine their individual style when communicating with patients. They will strive to create ethically sounds relationships with patients, the physician team and supporting hospital personnel. They will create effective written communications through accurate, complete, and legible notes. They will exhibit listening skills appropriate to patient-centered interviewing and communication. Residents will recognize verbal and nonverbal cues from patients.

2. PGY-2 and -3 residents will also exhibit team leadership skills through effective communication as manager of a team. PGY2 residents are expected to assist junior peers, medical students, and other hospital personnel to form professional relationships with support staff. Residents will respond to feedback in an appropriate manner and make necessary behavioral changes.

D. Professionalism.

All residents will demonstrate integrity, accountability, respect, compassion, patient advocacy, and dedication to patient care that supercedes self-interest. Residents will demonstrate a commitment to excellence and continuous professional development. They will be punctual and prepared for teaching sessions. Residents will demonstrate a commitment to ethical principles pertaining to provision or withholding of clinical care, confidentiality of patient information, and informed consent. Residents are expected to show sensitivity and responsiveness to patients' culture, age, gender and disabilities.

E. Practice Based Learning and Improvement

1. PGY-1 residents will use hospital and West Virginia

to show sensitivity and responsiveness to patients' culture, age, gender and disabilities.

E. Practice Based Learning and Improvement

1. PGY-1 residents will use hospital and West Virginia University library resources to critically appraise medical literature and apply evidence to patient care. They will use hand-held computers, desktop PC's and Internet electronic references to support patient care and self-education. They will model these behaviors to assist medical students in their own acquisition of knowledge through technology.

2. PGY-2 residents will in addition consistently seek out and analyze data on practice experience, identify areas for improvement in knowledge or patient care performance and make appropriate adjustments. They will regularly demonstrate knowledge of the impact of study design on validity or applicability to individual practice.

3. PGY-3 residents will additionally model independent learning and development.

F. Systems Based Practice.

1. PGY-1 residents will be sensitive to health care costs while striving to provide quality care. They will begin to effectively coordinate care with other health care professionals as required for patient needs.

2. PGY-2 residents, in addition to the above, will consistently understand and adopt available clinical practice guidelines and recognize the limitations of these guidelines. They will work with patient care managers, discharge coordinators and social workers to coordinate and improve patient care and outcomes.

3. PGY3 residents, in addition, will enlist social and other out-of-hospital resources to assist patients with therapeutic plans. PGY-3 residents are expected to model cost-effective therapy.

VII. Research

A. On-going research projects

Goals and Responsibilities of Pulmonary and Critical Care Medicine Fellows during MICU Rotation

Goals and Responsibilities of Pulmonary/Critical Care Medicine Fellows During MICU Rotation

Goals and Objectives: The critical care rotation exposes fellows to patients with a broad variety of unstable, life-threatening medical illnesses. Fellows will learn the basic tenets of stabilization of critically ill patients, and understand the differential diagnosis and appropriate diagnostic work ups of such patient. They will function within multidisciplinary teams to provide care that is timely, appropriate, and takes into account patient or family preferences.

Rotation Competency Objectives

a. **Patient Care** – History taking, physical exam, charting, procedures, medical decision making, clinical judgment and management plans. Fellows must be familiar with all MICU service patients.
b. **Medical Knowledge** – The fellow will acquire knowledge, problem solving ability, practical skills and an attitude applicable to the care of critically ill patients.
c. **Interpersonal and Communication Skills** – Fellows will develop and refine their individual style when communicating with patients. The will strive to create ethically sound relationships with patients, the physician team and supporting hospital personnel. They will create effective written communications through accurate, complete, and legible notes, they will exhibit listening skills appropriate to patient-centered interviewing and communication. Residents will recognize verbal and nonverbal cues from patients.
d. **Professionalism** – The fellow will demonstrate integrity, accountability, respect, compassion, patient advocacy, and dedication to patient care that supercedes self-interest. The fellow will demonstrate a commitment to excellence and continuous professional development. They will be punctual and prepared for teaching sessions. Residents will demonstrate a commitment to ethical principles pertaining to provision or withholding of clinical care, confidentiality of patient information, and informed consent. Fellows are expected to show sensitivity and responsiveness to patients' culture, age, gender and disabilities.
e. **Practice Based Learning and Improvement** – Fellows will utilize library resources to critically appraise medical literature and apply evidence to patient cares. Hand held computers, desktop PC's and Internet electronics reference will be utilized to support patient care and self education. Fellow will additionally model independent learning and development.
f. **System Based Practice** – Fellows will be sensitive to health care costs while striving to provide quality care. They will effectively coordinate care with other health care professionals as required for patient needs.
g. **Participation in the daily rounds.**
h. **Participation in research activities.**
i. **Conducting M&M conferences and generating the monthly report.**

Orientation

MICU Physician Guidelines for Orientation

There is a charge nurse assigned for each shift in SICU and MICU. If there are issues that need to be addressed, please discuss with the bedside nurse first. If this does not resolve the issue, the charge nurse needs to be notified. The list of patients, the nurse caring for the patient and the charge nurse is posted on the grease board in each ICU. The staff consists of Unit Clerks, Clinical Associates, Support Associates and Registered Nurses.

All admissions and discharges to the SICU and MICU are negotiated between the primary service and the SICU or MICU team. The admission and discharge processes are facilitated through a bed coordinator or off shift coordinator via pager 1070.

Upon admission, every patient needs an admission note with history of present illnesses, past medical history, medications, allergies, etc., and a tentative diagnosis and plan of management. Daily progress notes should be written on every patient.

Any change in the patient condition should be reported to the Attending Physician.

Upon discharge, all patients need a discharge note.

All procedures (intubation, arterial lines, central lines, Swan Ganz catheters, etc.) must be discussed with the Attending Physician. The Attending Physician will then make a decision as to whether he/she needs to be present for the procedure. All procedures must be recorded in the progress note of the patient chart and include the date, time and attending physician's name.

Medical students are not allowed to perform any invasive procedures, without the direct supervision and authorization of a resident or staff.

All procedures should be communicated and coordinated with nursing staff. If attempting to place a line is unsuccessful after 3 attempts, the expectation is that assistance with be obtained from a more senior physician (Fellow or Attending).

The daily management of Trauma patient will be undertaken by the SICU team. The management of MICU patients will be by the MICU team unless otherwise specified. Neurosurgical, ENT, Orthopedic and OB-GYN patients will be managed by the respective service expect for ventilatory management and line placement.

All unstable patients admitted to an overflow unit, ie: CTU, CCU, PAR are still under the same criteria as SICU or MICU.

Daily rounding starts between 7:00-7:30 daily; patient status including laboratory data should be gathered and presented during rounds.

Ventilator changes should only be made by an RRT assigned to the units. Changes in ventilatory settings will be ordered by the ICU team. The resident ordering these changes must notify the nurse taking care of the patient.

All orders must be done via CHIP system by the physician. Verbal orders are only taken under emergency situations.

The registered nurse monitors all IV lines. They man NOT manipulate, reposition or remove any PA catheters. The nurse may remove radial arterial lines and femoral triple lumens only.

If there are any questions, refer to each unit specific policy manual.

ICU Guidelines and Protocols

Guidelines for the Management of Community Acquired Pneumonia in Adults in ICU

(Based on IDSA/ATS guidelines on management of Community Acquired Pneumonia, 2007)

Most common etiologies of community-acquired pneumonia

Patient type	Etiology
Outpatient	Streptococcus pneumoniae Mycoplasma pneumoniae Haemophilus influenzae Chlamydophila pneumoniae Respiratory viruses[a]
Inpatient (non-ICU)	S. pneumoniae M. pneumoniae C. pneumoniae H. influenzae Legionella species Aspiration Respiratory viruses[a]
Inpatient (ICU)	S. pneumoniae Staphylococcus aureus Legionella species Gram-negative bacilli H. influenza

NOTE
a Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

Criteria for severe community-acquired pneumonia

Minor criteria[a]
Respiratory rate [b] >30 breaths/min
PaO2/FiO2 ratio [b] <250
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN level, >20 mg/dL)
Leukopenia [c] (WBC count, <4000 cells/mm3)
Thrombocytopenia (platelet count, <100,000 cells/mm3)
Hypothermia (core temperature, <36 C)
Hypotension requiring aggressive fluid resuscitation

Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors

NOTE
BUN, blood urea nitrogen; PaO2/FiO2, arterial oxygen pressure/fraction of inspired oxygen; WBC, white blood cell.
a. Other criteria to consider include hypoglycemia (in non diabetic patients), acute alcoholism/alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.
b. A need for noninvasive ventilation can substitute for a respiratory rate >30 breaths/min or a PaO2/FiO2 ratio <250.
c. As a result of infection alone

Recommended empirical antibiotics for community acquired pneumonia in ICU

A b-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin (level II evidence)
or
a respiratory fluoroquinolone (level I evidence) (strong recommendation) (for penicillin-allergic patients, a respiratory fluoroquinolone
and aztreonam are recommended)

Special concerns

If Pseudomonas is a consideration

An antipneumococcal, antipseudomonal b-lactam (piperacillintazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg)
or
The above b-lactam plus an aminoglycoside and azithromycin
or
The above b-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients,substitute aztreonam for above b-lactam)
(moderate recommendation; level III evidence)

If CA-MRSA is a consideration, add vancomycin or linezolid
(moderate recommendation; level III evidence)

Guidelines for the Management of Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia in Adults in ICU

(Based on ATS guidelines, Am J Respir Crit Care Med Vol 171. pp 388–416, 2005)

Overview of management strategies for a patient with suspected hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), or healthcare-associated pneumonia (HCAP)

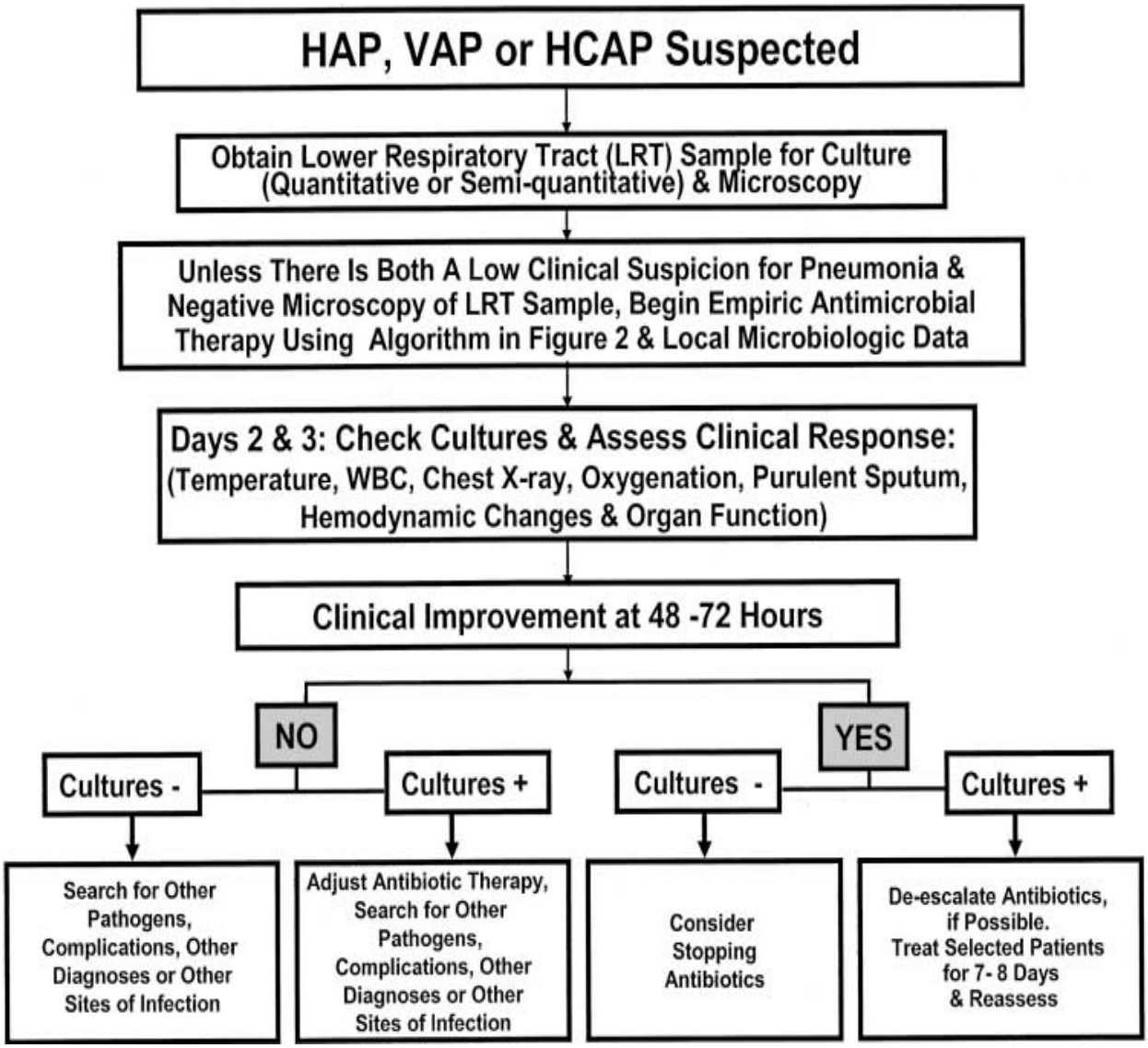


Table 2
Risk Factors for Multidrug Resistant Pathogens causing Hospital-acquired pneumonia, Ventilator-associated pneumonia and Healthcare-associated pneumonia

- Antimicrobial therapy in preceding 90 d
- Current hospitalization of 5 d or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP:
  - Hospitalization for 2 d or more in the preceding 90 d
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 d
  - Home wound care
  - Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

Algorithm for initiating empiric antibiotic therapy for hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP)

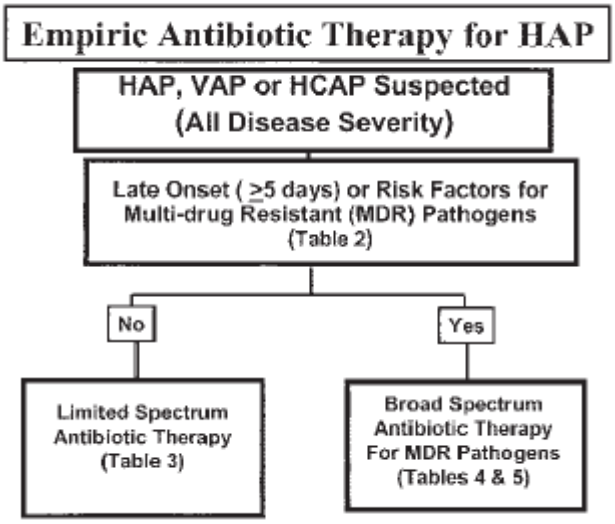


Table 3
Initial Empiric Antibiotic therapy for hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP) with no known risk factors for Multidrug-resistant pathogens, early onset

Potential Pathogen:	Recommended Antibiotic:
Streptococcus pneumoniae	Ceftriaxone
Haemophilus influenzae	or
Methicillin-sensitive Staphylococcus aureus	Levofloxacin, moxifloxacin, or ciprofloxacin
Antibiotic-sensitive enteric gram-negative bacilli	or
-Escherichia coli	Ampicillin/sulbactam
-Klebsiella pneumonia	or
-Enterobacter species	Ertapenem
-Proteus species	
-Serratia marcescens	

Table 4
Initial Empiric Antibiotic therapy for hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP) with late onset disease or risk factors for Multidrug-resistant pathogens

Potential Pathogens:	Combination Antibiotic Therapy:
Pathogens listed in Table 3 and	Antipseudomonal cephalosporin
MDR pathogens	(cefepime, ceftazidime)
-Pseudomonas aeruginosa	or
-Klebsiella pneumoniae (ESBL) †	
-Acinetobacter species†	Antipseudomonal carbepenem
	(imipenem or meropenem)
	or
	B-Lactam/B-lactamase inhibitor
	(piperacillin–tazobactam)
	plus
	Antipseudomonal fluoroquinolone†
	(ciprofloxacin or levofloxacin)
	or
	Aminoglycoside
	(amikacin, gentamicin, or
	tobramycin)
	plus
Methicillin-resistant Staphylococcus	Linezolid or vancomycin‡
aureus (MRSA)	
Legionella pneumophila†	

† If an ESBL_ strain, such as *K. pneumoniae*, or an *Acinetobacter* species is suspected, a carbepenem is a reliable choice. If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macolide (e.g., azithromycin)

or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.
‡ If MRSA risk factors are present or there is a high incidence locally.

WVUH ANTIBIOTIC CHOICE FOR VENTILATOR-ASSOCIATED PNEUMONIAS IN THE ICU

Note: All doses are for normal renal and liver function. Please refer to the pocket antimicrobial guide or the WVUH Antimicrobial Guidance website for help in patients with allergies to the specified agents. Pharmacists can also assist with alternative choices and dosing.

Early Onset, No aspiration (<5 days):

Ceftriaxone 2Gm IV x 1 then 1Gm IV q24h plus (Azithromycin 500mg IV/PO q24h OR doxycycline 100mg IV/PO q12h)

Early Onset, Aspiration suspected:

Ampicillin/Sulbactam (Unasyn) 3Gm IV q6h
Or
Ertapenem 1Gm IV q24h

Late Onset (>5 days) Antibiotic Rotation:

Choose a Gram positive agent and 1 beta-lactam Gram negative agent +/- tobramycin

Gram Positive Coverage

Start Date	Drug/Dose	
January 2013	**Vancomycin** IV (Trough ≥15)[##]	De-escalate at 72 hours w/negative cultures to **NO ANTIBIOTICS or Nafcillin IV 2gm q4h if not MRSA or MRSE**
January 2014	**Linezolid** IV/PO 600mg q12h	
July 2014	**Vancomycin** IV (Trough ≥15)[##]	

Gram Negative Coverage

1st agent:

Start Date	Drug/Dose	De-escalate at 72hrs w/**negative cultures** to **NO ANTIBIOTICS or the following:**
July 2013	**Piperacillin/tazobactam** 3.375Gm IV q8h infused over 4 hrs (Alt. 4.5Gm IV q6h)	**Ampicillin/Sulbactam** 3Gm IV q6h
October 2013	**Cefepime** 2Gm IV q8h infused over 3 hrs	**Ceftriaxone** 2 Gm IV q24h
January 2014	**Meropenem** 1Gm IV q8h infused over 3 hrs	**Ertapenem** 1Gm IV q24h
April 2014	**Piperacillin/tazobactam** 3.375Gm IV q8h infused over 4 hrs (alt. 4.5Gm IV q6h)	**Ampicillin/Sulbactam** 3Gm IV q6h
July 2014	**Cefepime** 2Gm IV q8h infused over 3 hrs	**Ceftriaxone** 2 Gm IV q24h
October 2014	**Meropenem** 1Gm IV q8h infused over 3 hrs	**Ertapenem** 1Gm IV q24h

2nd Agent:

Tobramycin 5-7mg/kg IBW IV q24h**

**Contact pharmacy for assistance with appropriate dosing or alternatives in renal or liver dysfunction. Fluoroquinolone use is discouraged due to sensitivity rates and association with Clostridium difficile. If a microbial pathogen is isolated, attempt to simplify the regimen to its narrowest spectrum while keeping in the same antimicrobial class (e.g., Penicillins, Cephalosporins, Beta lactam/beta lactamase inhibitor)

-VANCOMYCIN DOSING -Refer to WVUH Antibiotic website or consult pharmacist for recommendation.

Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

(Based on SCCM guidelines, Crit Care Med. 2013 Jan;41(1):263-306)

TABLE 3. Pharmacology of Opiate Analgesics (1, 128, 440, 472)

Opiates	Equi-Analgesic Dose (mg) IV	Equi-Analgesic Dose (mg) PO	Onset (IV)	Elimination Half-Life	Context-Sensitive Half-Life	Metabolic Pathway
Fentanyl	0.1	N/A	1–2 min	2–4 hr	200 min (6hr infusion); 300 min (12 hr infusion)[a]	N-dealkylation CYP3A4/5 substrate
Hydromorphone	1.5	7.5	5–15 min	2–3 hr	N/A	Glucuronidation
Morphine	10	30	5–10 min	3–4 hr	N/A	Glucuronidation
Methadone	N/A[c]	N/A[c]	1–3 d	15–60 hr	N/A	N-demethylation CYP3A4/5, 2D6, 2B6, 1A2 substrate
Remifentanil	N/A	N/A	1–3 min	3–10 min	3–4 min	Hydrolysis by plasma esterases

PO = oral; N/A = not applicable; IBW = ideal body weight.

[a]After 12 hrs, and in cases of end-organ dysfunction, the context-sensitive half-life increases unpredictably.

[b]May increase dose to extend dosing interval; hydromorphone 0.5 mg IV every 3 hrs, or morphine 4–8 mg IV every 3–4 hrs.

[c]Equianalgesic dosing tables may underestimate the potency of methadone. The morphine- or hydromorphone-to-methadone conversion ratio increases (i.e., the potency of methadone increases) as the dose of morphine or hydromorphone increases. The relative analgesic potency ratio of oral to parenteral methadone is 2:1, but the confidence intervals are wide.

[d]QTc is the Q-T interval (corrected) of the electrocardiographic tracing.

TABLE 3 (Continued).

Active Metabolites	Intermittent Dosing	IV Infusion Rates	Side Effects and Other Information
None	0.35–0.5 µg/kg IV q0.5–1 hr	0.7–10 µg/kg/hr	Less hypotension than with morphine. Accumulation with hepatic impairment.
None	0.2–0.6 mg IV q1–2 hr[b]	0.5–3 mg/hr	Therapeutic option in patients tolerant to morphine/fentanyl. Accumulation with hepatic/renal impairment.
6- and 3-glucuronide metabolite	2–4 mg IV q1–2 hr[b]	2–30 mg/hr	Accumulation with hepatic/renal impairment. Histamine release.
N-demethylated derivative	IV/PO: 10–40 mg q6–12 hr IV: 2.5–10 mg q8–12 hr	Not recommended	May be used to slow the development of tolerance where there is an escalation of opioid dosing requirements. Unpredictable pharmacokinetics; unpredictable pharmacodynamics in opiate naïve patients. Monitor QTc.[d]
None	N/A	Loading dose: 1.5 µg/kg IV Maintenance dose: 0.5–15 µg/kg/hr IV	No accumulation in hepatic/renal failure. Use IBW if body weight >130% IBW.

TABLE 4. Pharmacology of Nonopiate Analgesics (1, 91, 132, 440)

Nonopiates (Route)	Onset	Elimination Half-Life	Metabolic Pathway	Active Metabolites
Ketamine (IV)	30–40 sec	2–3 hr	N-demethylation	Norketamine
Acetaminophen (PO) Acetaminophen (PR)	30–60 min variable	2–4 hr	Glucuronidation, sulfonation	None
Acetaminophen (IV)	5–10 min	2 hr	Glucuronidation, sulfonation	None
Ketorolac[a] (IM/IV)	10 min	2.4–8.6 hr	Hydroxylation, conjugation/ renal excretion	None
Ibuprofen (IV)	N/A	2.2–2.4 hr	Oxidation	None
Ibuprofen (PO)	25 min	1.8–2.5 hr	Oxidation	None
Gabapentin (PO)	N/A	5–7 hr	Renal excretion	None
Carbamazepine immediate release (PO)	4–5 hr	25–65 hrs initially, then 12–17 hr	Oxidation	None

PO = orally; PR = rectally; max = maximum; IM = intramuscular; N/A = not applicable.
[a]For patients > 65 yr or < 50 kg, 15 mg IV/IM every 6 hrs to a maximum dose of 60 mg/day for 5 days.

TABLE 4 (Continued).

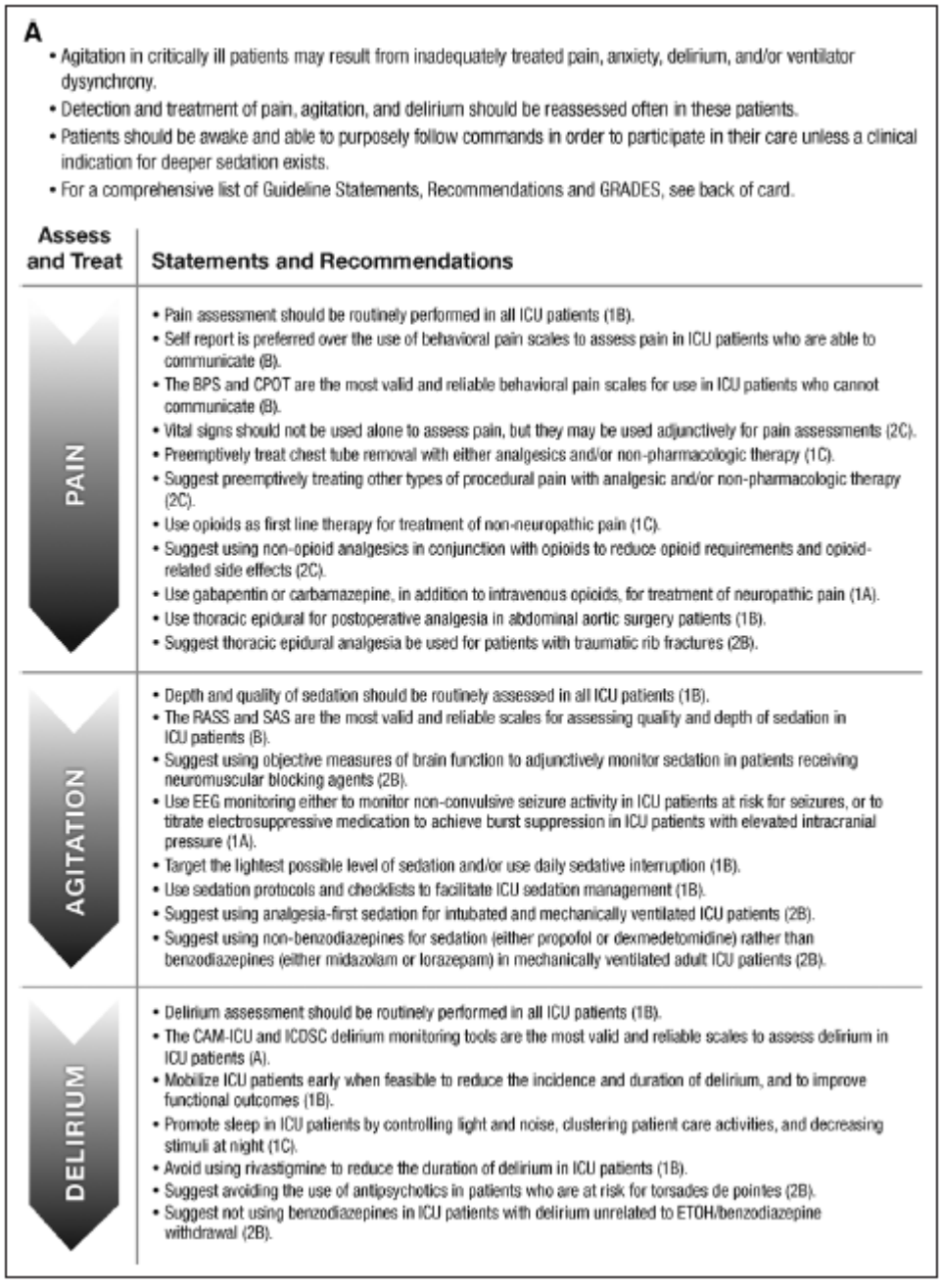
Dosing	Side Effects and Other Information
Loading dose 0.1–0.5 mg/kg IV followed by 0.05–0.4 mg/kg/hr	Attenuates the development of acute tolerance to opioids. May cause hallucinations and other psychological disturbances.
325–1000 mg every 4–6 hr; max dose ≤ 4 g/day)	May be contraindicated in patients with significant hepatic dysfunction.
650 mg IV every 4 hrs – 1000 mg IV every 6 hr; max dose ≤ 4 g/day	
30 mg IM/IV, then 15–30 mg IM/IV every 6 hr up to 5 days; max dose = 120 mg/day × 5 days	Avoid nonsteroidal anti-inflammatory drugs in following conditions: renal dysfunction; gastrointestinal bleeding; platelet abnormality; concomitant angiotensin converting enzyme inhibitor therapy, congestive heart failure, cirrhosis, asthma. Contraindicated for the treatment of perioperative pain in coronary artery bypass graft surgery.
400–800 mg IV every 6 hr infused over > 30 mins; max dose = 3.2 g/day	Avoid nonsteroidal anti-inflammatory drugs in following conditions: renal dysfunction; gastrointestinal bleeding; platelet abnormality; concomitant angiotensin converting enzyme inhibitor therapy, congestive heart failure, cirrhosis, asthma. Contraindicated for the treatment of perioperative pain in coronary artery bypass graft surgery.
400 mg PO every 4 hrs; max dose = 2.4 g/day	
Starting dose = 100 mg PO three times daily; maintenance dose = 900–3600 mg/day in 3 divided doses	Side effects: (common) sedation, confusion, dizziness, ataxia. Adjust dosing in renal failure pts. Abrupt discontinuation associated with drug withdrawl syndrome, seizures.
Starting dose = 50–100 mg PO bid; maintenance dose = 100–200 mg every 4–6 hr; max dose = 1200 mg/day	Side effects: (common) nystagmus, dizziness, diplopia, lightheadedness, lethargy; (rare) aplastic anemia, and agranulocytosis; Stevens–Johnson syndrome or toxic epidermal necrolysis with HLA-B1502 gene. Multiple drug interactions due to hepatic enzyme induction.

TABLE 6. Clinical Pharmacology of Sedative Medications (1)

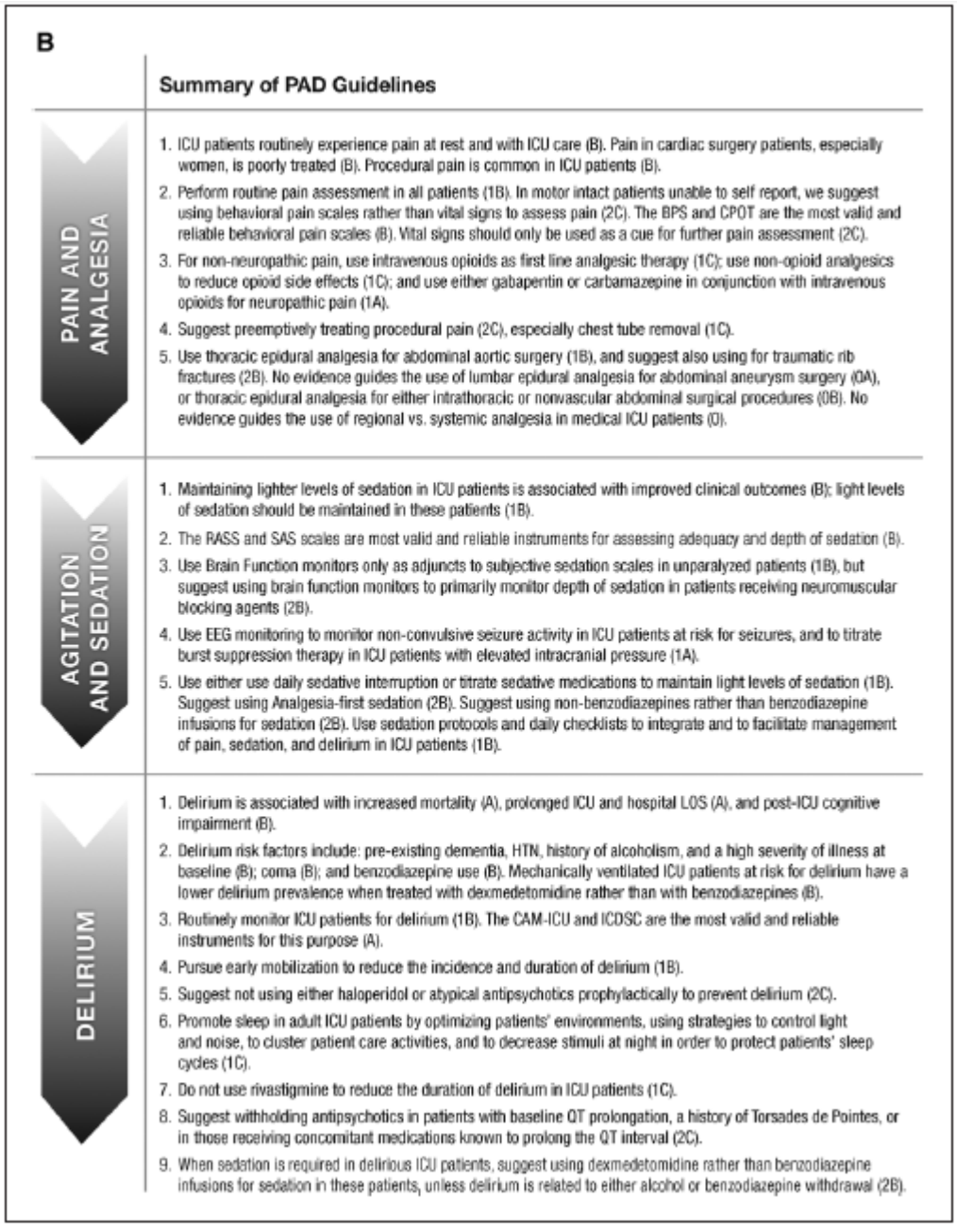
Agent	Onset After IV Loading Dose	Elimination Half-Life	Active Metabolites	Loading Dose (IV)	Maintenance Dosing (IV)	Adverse Effects
Midazolam	2–5 min	3–11 hr	Yes[a]	0.01–0.05 mg/kg over several minutes	0.02–0.1 mg/kg/hr	Respiratory depression, hypotension
Lorazepam	15–20 min	8–15 hr	None	0.02–0.04 mg/kg (≤ 2 mg)	0.02–0.06 mg/kg q2–6 hr prn or 0.01–0.1 mg/kg/hr (≤10 mg/hr)	Respiratory depression, hypotension; propylene glycol-related acidosis, nephrotoxicity
Diazepam	2–5 min	20–120 hr	Yes[a]	5–10 mg	0.03–0.1 mg/kg q0.5–6hr prn	Respiratory depression, hypotension, phlebitis[e]
Propofol	1–2 min	Short-term use = 3–12 hr Long-term use = 50 ± 18.6 hr	None	5 μg/kg/min over 5 min[b]	5–50 μg/kg/min	Pain on injection[f], hypotension, respiratory depression, hypertriglyceridemia, pancreatitis, allergic reactions, propofol-related infusion syndrome; deep sedation with propofol is associated with significantly longer emergence times than with light sedation
Dexmedetomidine	5–10 min	1.8–3.1 hr	None	1 μg/kg over 10 min[c]	0.2–0.7 μg/kg/hr[d]	Bradycardia, hypotension; hypertension with loading dose; loss of airway reflexes

[a]Active metabolites prolong sedation, especially in patients with renal failure.
[b]Administer IV loading dose of propofol only in those patients in whom hypotension is unlikely to occur.
[c]Avoid IV loading doses of dexmedetomidine in hemodynamically unstable patients.
[d]Dexmedetomidine maintenance infusion rate may be increased to 1.5 μg/kg/h as tolerated.
[e]Phlebitis occurs when diazepam is injected into peripheral veins.
[f]Pain at the injection site occurs commonly when propofol is administered through peripheral veins.

Recommendations for the Management of Pain, Agitation, and Delirium
Figure 1



Recommendations for the Management of Pain, Agitation, and Delirium
Figure 2



Management of Neuromuscular Blockade in the Adult ICU

*All attempts to use alternatives to should be made before deciding to use neuromuscular blocking agents.

Be aware that prolonged neuromuscular weakness is associated with use of these agents. Combination therapy with steroids and/or aminoglycosides will further add to this syndrome.

Neuromuscular blocking agents produce skeletal muscle relaxation and paralysis. They have **no** amnestic, analgesic, or sedative properties.

All patients receiving neuromuscular blockade should be receiving continuous sedation and analgesic therapy during administration of neuromuscular blockers. Bedside nurse and house staff physician must evaluate patient.

DRUG OF CHOICE

CISATRACURIUM
(Drip: 1mg/ml)

Bolus: 0.1mg/kg, then administer continuous infusion

Continuous Infusion: 1-2mcg/kg/min

Titrate to effect using train of four nerve stimulation monitoring (maximum of 2-4 twitches) or until optimal ventilation/oxygenation is achieved.

Most patients are to receive a "drug free holiday" at 0800. The paralyzing agent is to be turned off, allowing the patient to come out of paralysis to assess for prolonged paralysis and to assess if the level of sedation and pain control are adequate.

DAILY INTERRUPTION OF SEDATIVE INFUSIONS IN CRITICALLY ILL PATIENTS UNDERGOING MECHANICAL VENTILATION

JOHN P. KRESS, M.D., ANNE S. POHLMAN, R.N., MICHAEL F. O'CONNOR, M.D., AND JESSE B. HALL, M.D.

ABSTRACT

Background Continuous infusions of sedative drugs in the intensive care unit may prolong the duration of mechanical ventilation, prolong the length of stay in the intensive care unit and the hospital, impede efforts to perform daily neurologic examinations, and increase the need for tests to assess alterations in mental status. Whether regular interruption of such infusions might accelerate recovery is not known.

Methods We conducted a randomized, controlled trial involving 128 adult patients who were receiving mechanical ventilation and continuous infusions of sedative drugs in a medical intensive care unit. In the intervention group, the sedative infusions were interrupted until the patients were awake, on a daily basis; in the control group, the infusions were interrupted only at the discretion of the clinicians in the intensive care unit.

Results The median duration of mechanical ventilation was 4.9 days in the intervention group, as compared with 7.3 days in the control group (P=0.004), and the median length of stay in the intensive care unit was 6.4 days as compared with 9.9 days, respectively (P=0.02). Six of the patients in the intervention group (9 percent) underwent diagnostic testing to assess changes in mental status, as compared with 16 of the patients in the control group (27 percent, P=0.02). Complications (e.g., removal of the endotracheal tube by the patient) occurred in three of the patients in the intervention group (4 percent) and four of the patients in the control group (7 percent, P=0.88).

Conclusions In patients who are receiving mechanical ventilation, daily interruption of sedative-drug infusions decreases the duration of mechanical ventilation and the length of stay in the intensive care unit. (N Engl J Med 2000;342:1471-7.)

CRITICALLY ill patients who require mechanical ventilation are often given continuous intravenous infusions of sedative drugs to treat anxiety and agitation and to facilitate their care. Benzodiazepines are the agents most commonly given,[1,2] but some patients are given other nonanalgesic sedatives, such as propofol[3,4] or haloperidol.[5] Opiates are often given as well, since nonopiate sedatives have no analgesic properties. New approaches to mechanical ventilation, often involving the use of permissive hypercapnia (i.e., allowing the partial pressure of arterial carbon dioxide to reach 50 mm Hg or higher), can cause patients substantial discomfort, necessitating high levels of sedation.[6,7]

In many intensive care units, sedatives are infused continuously.[1,2] As compared with intermittent bolus infusion, this approach provides a more constant level of sedation and may increase patients' comfort.[8,9] However, administration of sedatives by continuous infusion has been identified as an independent predictor of a longer duration of mechanical ventilation as well as a longer stay in the intensive care unit and in the hospital.[10]

Continuous infusion of sedatives has other disadvantages. Extended sedation may limit clinicians' ability to interpret physical examinations. It may be difficult to distinguish changes in mental status that are due to the action of a sedative from those that are due to neurologic injury. Therefore, clinicians may be compelled to order diagnostic studies to rule out new neurologic injury when patients do not awaken rapidly after the sedative infusion is discontinued.

The benefit of administering sedatives by continuous infusion must be balanced against these disadvantages. Daily interruption of sedative infusions to allow patients to "wake up" may improve the situation by allowing clinicians to streamline the administration of sedatives while ensuring optimal comfort for patients. We undertook this study to determine whether daily interruption of sedative infusions in critically ill patients receiving mechanical ventilation would decrease the duration of mechanical ventilation and the length of stay in the intensive care unit and in the hospital.

METHODS

Patients

We studied patients in the medical intensive care unit who were intubated and receiving mechanical ventilation and who were deemed by the intensive care unit team to require sedation by continuous intravenous infusion. Included among these patients were all those who showed agitation or discomfort after recovering from the effects of the drugs used to facilitate endotracheal intubation (e.g., thiopental or etomidate). The exclusion criteria were pregnancy, transfer from an outside institution where sedatives had already been administered, and admission after resuscitation from cardiac arrest. The patients were randomly assigned to one of two strategies: daily interruption of the infusion of sedatives begin-

From the Department of Medicine, Section of Pulmonary and Critical Care (J.P.K., A.S.P., J.B.H.), and the Department of Anesthesia and Critical Care (M.F.O., J.B.H.), University of Chicago, Chicago. Address reprint requests to Dr. Hall at the University of Chicago, Department of Medicine, Section of Pulmonary and Critical Care, MC 6026, Chicago IL 60637, or at jhall@medicine.bsd.uchicago.edu.

ning 48 hours after enrollment (the intervention group) or continuous infusion of sedatives with interruption only at the discretion of the intensive care unit team (the control group). Within each group, the patients were then randomly assigned to receive either midazolam or propofol. The random assignments were generated by computer and then concealed in sealed envelopes. Patients' assignment to the intervention group or the control group was known only to the study investigators, but the sedatives were given on an open-label basis.

All four subgroups simultaneously received an infusion of morphine for analgesia. The infusion of the combination of a nonanalgesic sedative drug (propofol or midazolam) and morphine will henceforth be referred to as the infusion of sedative drugs. The protocols for the infusion of sedatives are shown in Table 1. Nurses adjusted the dosage and rate of infusion according to standard procedures at our institution (to achieve a score of 3 or 4 on the Ramsay sedation scale, which measures sedation on a scale of 1 [agitated or restless] to 6 [asleep and unresponsive to stimuli][11]).

Base-line demographic data, Acute Physiology and Chronic Health Evaluation (APACHE II) scores,[12] and the reason for admission to the intensive care unit were recorded for all patients. The number of patients with pulmonary edema, acute respiratory distress syndrome, or status asthmaticus who underwent ventilation with the use of permissive hypercapnia (intentional hypoventilation to allow an arterial carbon dioxide tension of ≥50 mm Hg) was also recorded. The paralytic drug cisatracurium was given to patients with the acute respiratory distress syndrome or status asthmaticus whose ventilation was deemed ineffective while they were receiving the sedative infusions.

The study was approved by the institutional review board at the University of Chicago. The requirement for consent from patients was waived because the intervention, though not routinely applied, was within the established standard of care at our institution.

Study Protocol

In the intervention group, an investigator not directly involved in the patients' care interrupted the infusion of midazolam or propofol and the infusion of morphine simultaneously on a daily basis until the patients were awake and could follow instructions or until they became uncomfortable or agitated and were deemed to require the resumption of sedation. If a patient was receiving a paralytic drug, the sedative infusion was not interrupted. A research nurse who was not directly involved in the patients' care evaluated the patients each day throughout the period when infusions were stopped until the patients were either awake or uncomfortable and in need of resumed sedation. This nurse immediately contacted a study physician when a patient awakened, at which time the study physician examined the patient and decided whether to resume the infusions. For the patients in the intervention group who were receiving paralytic drugs, the sedative infusions were stopped daily (after administration of the paralytic drug had been stopped) in a manner identical to that for the patients in the intervention group who were not receiving paralytic drugs. The sedative infusions were started again after the patient was awake or, if agitation prevented successful waking, at half the previous rates and were adjusted according to the need for sedation.

The patients in the control group were monitored each day by research staff, and the total daily doses of sedative drugs infused were recorded. The adjustment of the dosage of sedative drugs in the control group was left to the discretion of the intensive care unit team. Apart from daily interruption and resumption of sedative-drug infusions in the intervention group, all other decisions regarding patient care were made by the intensive care unit team.

Each day, we assessed each patient's mental status with respect to wakefulness. A patient was considered "awake" if he or she was able to perform at least three of the following four actions, which could be assessed objectively: open the eyes in response to a voice, use the eyes to follow the investigator on request, squeeze a hand on request, and stick out the tongue on request.[13] The percentage of days on which the patient was classified as awake (the number of days awake divided by the total number of days during which sedative-drug infusions were given) was recorded. Patients were considered to have been awake on any given day if they had been awake at any time during that day.

Table 1. Protocols for the Infusion of Sedative Drugs in the Study Patients.*

Assigned Sedative Drug	Protocol
Midazolam	Midazolam: initial intravenous bolus of 0.5–5 mg every 1–5 min as needed
	Midazolam: continuous infusion at 1–2 mg/hr; dosage to be increased in increments of 1–2 mg/hr until adequate sedation is achieved
	Morphine: initial intravenous bolus of 2–10 mg as needed
	Morphine: continuous infusion at 1–5 mg/hr
Propofol	Propofol: continuous infusion at 5 μg/kg of body weight/min; dosage to be increased in increments of 5–10 μg/kg/min every 2 min until adequate sedation is achieved
	Morphine: initial intravenous bolus of 2–10 mg as needed
	Morphine: continuous infusion at 1–5 mg/hr

*The doses of sedatives and morphine were adjusted to achieve a score of 3 or 4 on the Ramsay sedation scale (on which 1 denotes anxious and agitated or restless or both; 2 cooperative, oriented, and tranquil; 3 responsive to commands only; 4 asleep, with a brisk response to a light glabellar tap or loud sound; 5 asleep, with a sluggish response to a light glabellar tap or loud sound; and 6 asleep, with no response to a light glabellar tap or loud sound). Morphine was given to ensure adequate analgesia; it was administered to all patients "as needed," according to the nurse's assessment of the level of analgesia (on a scale on which 1 denotes extreme pain, 2 severe pain, 3 moderate pain, 4 slight pain, and 5 no pain). Morphine was administered in response to a score of 1 to 4 and was continued until the pain was considered to be adequately controlled.

End Points

The primary end points of the study were the duration of mechanical ventilation, the length of stay in the intensive care unit, and the length of stay in the hospital. The total doses of either midazolam or propofol and of morphine administered were recorded, as were the average rates of infusion (calculated as total milligrams of drug per kilogram of body weight, divided by the total number of hours from the start of the infusion to its termination).

The use of neurologic tests (e.g., computed tomography [CT] of the brain, magnetic resonance imaging [MRI] of the brain, and lumbar puncture) was recorded, as were the numbers of patients requiring paralytic drugs, reintubation, noninvasive ventilation, or tracheostomy. Adverse events (e.g., removal of the endotracheal tube by the patient), transfer to a facility equipped to provide long-term ventilation, withdrawal of care (a change in care from curative measures to measures aimed at comfort), and death in the hospital were also recorded. The specific end points to be studied were not disclosed to any of the caregivers.

Statistical Analysis

Data were analyzed on an intention-to-treat basis. Patients who died during the first or second day in the intensive care unit and those from whom the endotracheal tube was successfully removed during the first or second day, before the sedative infusion could be interrupted, were not included in the analysis. All patients were followed until discharge from the hospital.

Nonparametric data were analyzed with Mann–Whitney U tests. These data are presented as median values (with 25th and 75th

percentiles). Nominal data were analyzed by chi-square analysis with Yates' continuity correction or by Fisher's exact test, as appropriate. Kaplan–Meier survival analysis[14] and Cox proportional-hazards analysis[15] were used to assess the effects of daily interruption of the sedative infusion on the duration of mechanical ventilation and on the length of stay in the intensive care unit and in the hospital. Cox proportional-hazards analysis was used to assess differences between the intervention group and the control group after adjustment for base-line variables, including age, sex, weight, APACHE II score, and type of respiratory failure (acute hypoxemic respiratory failure, such as that resulting from pulmonary edema or the acute respiratory distress syndrome; hypercapnic respiratory failure; or shock).[16] All statistical tests were two-sided.

RESULTS

Patients

A total of 150 patients were enrolled in the study; 75 were randomly assigned to the intervention group and 75 to the control group. Seven patients in the intervention group and 15 in the control group were excluded because either the endotracheal tube was removed or they died on the first or second day in the intensive care unit. Thus, 68 patients in the intervention group and 60 in the control group were included in the analyses. The demographic characteristics, APACHE II scores, rate of use of permissive hypercapnia during ventilation, and diagnoses on admission to the intensive care unit were similar in the two groups (Table 2). In the intervention group, 37 patients received midazolam and 31 received propofol, and in the control group 29 received midazolam and 31 received propofol. There were no demographic differences between these subgroups in either group (data not shown).

TABLE 2. CHARACTERISTICS OF THE STUDY PATIENTS ON ADMISSION TO THE INTENSIVE CARE UNIT.

VARIABLE	INTERVENTION GROUP (N=68)	CONTROL GROUP (N=60)	P VALUE
Age (yr)			0.57
Median	57	61	
Interquartile range	42–71	40–74	
Sex (no.)			0.56
Male	34	26	
Female	34	34	
Weight (kg)			0.70
Median	69.9	66.0	
Interquartile range	58.9–90.2	60.4–78.8	
APACHE II score*			0.30
Median	20	22	
Interquartile range	15–25	16–25	
Permissive hypercapnia (no.)	12	15	0.42
Diagnosis (no.)			
Acute respiratory distress syndrome or pulmonary edema	30	15	0.72
Chronic obstructive pulmonary disease or ventilatory failure	22	17	0.76
Asthma	4	3	0.86
Sepsis	10	15	0.21
Delirium	8	5	0.73
Hemorrhagic shock	1	3	0.52
Cardiogenic shock	2	2	0.70
Drug overdose	1	0	0.95

*APACHE II denotes Acute Physiology and Chronic Health Evaluation. The APACHE II is an assessment of the severity of illness, with possible scores ranging from 0 to 71 (increasing scores correlate with an increasing risk of in-hospital death).

Outcomes

In 18 of the 60 patients in the control group, the sedative infusions were stopped temporarily on days other than the final day of administration, and the percentage of days (other than the final day) on which the drugs were stopped ranged from 0 to 54 percent. The daily interruption of sedative infusions in the intervention group was associated with a significant decrease in the duration of mechanical ventilation; the median duration of mechanical ventilation in this group was 2.4 days shorter than it was in the control group (Table 3). Mechanical ventilation was discontinued earlier in the intervention group than in the control group (relative risk of extubation, 1.9; 95 percent confidence interval, 1.3 to 2.7; $P<0.001$) (Fig. 1). The median length of stay in the intensive care unit in the intervention group was shorter than it was in the control group by 3.5 days (relative risk of discharge, 1.6; 95 percent confidence interval, 1.1 to 2.3; $P=0.02$) (Fig. 2). The length of stay in the hospital did not differ between the two groups (Table 3).

Among the patients receiving midazolam, the total dose of this sedative was lower in the intervention group than in the control group, as was the total dose of morphine (Table 3). In contrast, among the patients receiving propofol, there were no significant differences between the intervention and the control groups in the total dose of propofol or the total dose of morphine.

The percentage of days during which patients were awake while receiving a sedative infusion was greater in the intervention group than in the control group (85.5 percent vs. 9.0 percent, $P<0.001$). Fewer diagnostic tests to assess changes in mental status were performed in the intervention group (6 CT scans of the brain) than in the control group (13 CT scans of the brain, 2 MRI scans of the brain, and 1 lumbar puncture; $P=0.02$). Only 4 of the 16 tests in the control group and 3 of the 6 tests in the intervention group provided an explanation (e.g., intracranial hemorrhage) for the changes in mental status.

Only 7 patients in the intervention group never awakened during their stay in the intensive care unit, as compared with 15 patients in the control group ($P=0.05$). Of these patients, 6 in the intervention group and 13 in the control group died in a coma; the others were transferred to facilities equipped to provide long-term ventilation. There were no significant differences between the two groups in the number of other adverse events (in the intervention group, two patients removed the endotracheal tube and one

Table 3. The Duration of Mechanical Ventilation, Length of Stay in the Intensive Care Unit and the Hospital, and Doses of Sedative Drugs and Morphine, According to Study Group.*

Variable	Intervention Group (N=68)	Control Group (N=60)	P Value
	median (interquartile range)		
Duration of mechanical ventilation (days)	4.9 (2.5–8.6)	7.3 (3.4–16.1)	0.004
Length of stay (days)			
Intensive care unit	6.4 (3.9–12.0)	9.9 (4.7–17.9)	0.02
Hospital	13.3 (7.3–20.0)	16.9 (8.5–26.6)	0.19
Midazolam subgroup (no. of patients)	37	29	
Total dose of midazolam (mg)	229.8 (59–491)	425.5 (208–824)	0.05
Average rate of midazolam infusion (mg/kg/hr)	0.032 (0.02–0.05)	0.054 (0.03–0.07)	0.06
Total dose of morphine (mg)	205 (68–393)	481 (239–748)	0.009
Average rate of morphine infusion (mg/kg/hr)	0.027 (0.02–0.04)	0.05 (0.04–0.07)	0.004
Propofol subgroup (no. of patients)	31	31	
Total dose of propofol (mg)	15,150 (3983–34,125)	17,588 (4769–35,619)	0.54
Average rate of propofol infusion (mg/kg/hr)	1.9 (0.9–2.6)	1.4 (0.9–2.4)	0.41
Total dose of morphine (mg)	352 (108–632)	382 (148–1053)	0.33
Average rate of morphine infusion (mg/kg/hr)	0.035 (0.02–0.07)	0.043 (0.02–0.07)	0.65

*Average rates of infusion were calculated as milligrams of drug per kilogram of body weight divided by the number of hours from the start of the infusion to its termination.

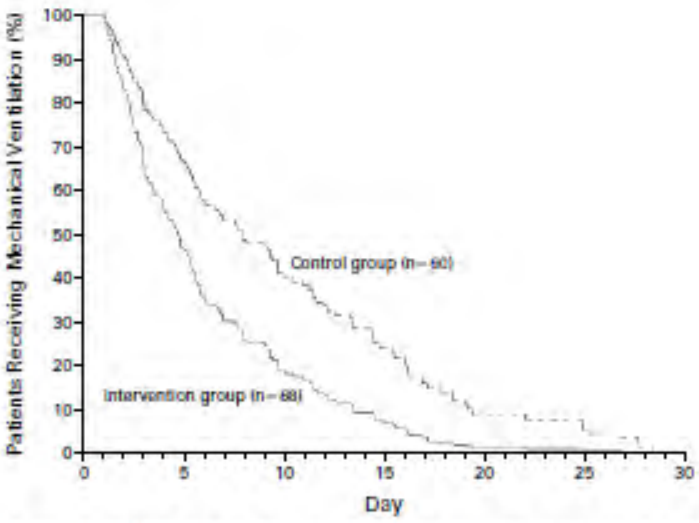


Figure 1. Kaplan–Meier Analysis of the Duration of Mechanical Ventilation, According to Study Group.

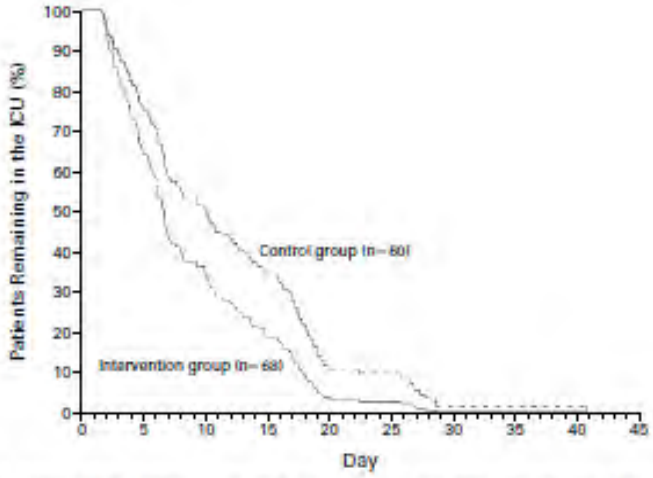


Figure 2. Kaplan–Meier Analysis of the Length of Stay in the Intensive Care Unit (ICU), According to Study Group.

After adjustment for base-line variables (age, sex, weight, APACHE II score, and type of respiratory failure), discharge from the intensive care unit (ICU) occurred earlier in the intervention group than in the control group (relative risk of discharge, 1.6; 95 percent confidence interval, 1.1 to 2.3; P=0.02).

pulled out a central venous catheter; in the control group, four patients removed the endotracheal tube) (P=0.88). Seven patients in each group were given cisatracurium (P=0.78), and five in each group required noninvasive ventilation after extubation (P=0.74). Twelve patients in the intervention group and 18 patients in the control group required reintubation (P=0.17), and 12 and 16, respectively, underwent tracheostomy (P=0.31). Nine patients in the intervention group and 12 in the control group were transferred to a facility equipped to provide long-term ventilation (P=0.43). The in-hospital mortality rate did not differ significantly between the two groups (36.0 percent in the intervention group and 46.7 percent in the control group, P=0.25), and care was withdrawn from 24 and 25 patients, respectively (P=1.00). Fifty-nine percent of the patients in the intervention group were discharged to their homes, as compared with 40 percent of the patients in the control group (P=0.06).

When the primary end points of the study (the duration of mechanical ventilation, the length of stay in the intensive care unit, and the length of stay in the hospital) were evaluated according to whether midazolam or propofol was given, no significant differences between the intervention and control groups were found (data not shown). In the intervention group, the average number of hours per day that patients received the sedative infusion was 22.8 among those given propofol, as compared with 18.7 among those given midazolam (P=0.05).

DISCUSSION

Sedatives are often given to patients who are receiving mechanical ventilation to alleviate their anxiety, decrease excessive oxygen consumption, and facilitate nursing care.[17] Administration of these drugs by continuous infusion offers a more consistent level of sedation than intermittent bolus administration and thus may improve patients' comfort.[9] In our experience, sedation is often difficult with intermittent administration, and such regimens can be taxing on nurses and can hamper other aspects of patient care.[17] However, a potential drawback to continuous infusions is the accumulation of the drug and accompanying delays in the improvement of mental status. We hypothesized that daily interruption of the sedative infusion would decrease these problems.

Care of critically ill patients is costly. In the United States in 1997, approximately $80.8 billion was spent on intensive care,[18] and about 10 percent of this amount was spent on drugs.[19] Ten to 15 percent of the drug costs resulted from the purchase of sedative drugs.[20] Thus, a conservative estimate of the yearly cost of sedative drugs administered in intensive care units in the United States, in 1997 dollars,[21] is between $0.8 billion and $1.2 billion, and the costs may be higher than that if the use of sedative drugs

increases the duration of mechanical ventilation and the length of stay in the intensive care unit.

In this study, daily interruption of the infusion of sedative drugs shortened the duration of mechanical ventilation by more than 2 days and the length of stay in the intensive care unit by 3.5 days. Reducing the duration of mechanical ventilation will probably cut costs — both monetary costs and those related to complications of mechanical ventilation, such as ventilator-associated pneumonia and barotrauma. Daily interruption of the sedative infusion is a practical, cost-effective intervention that can be readily performed by the nurses caring for patients in the intensive care unit. The results of neurologic assessments can then be relayed to physicians, and infusions of sedative drugs can be restarted and adjusted as needed by the nurses. Our results suggest that daily interruption of the sedative infusion provides acceptable sedation while minimizing adverse effects.

In addition, in our study, daily interruption of the sedative infusion reduced the total dose of midazolam administered by almost half. A trend toward the use of lower doses of benzodiazepines has previously been reported[13,22] and is at least partly related to the concomitant administration of opiates such as morphine. Benzodiazepines may enhance the analgesic effects of morphine,[23] and this synergism may decrease the doses of benzodiazepines needed to achieve adequate sedation. In our study, daily interruption of the sedative infusion did not alter the doses of propofol administered. The concentration of propofol in plasma declines rapidly after administration is discontinued,[24] and this is probably the reason why the daily period of drug stoppage in the intervention group was shorter among patients assigned to propofol than among those assigned to midazolam. Despite this difference, the patients were awake on more than 80 percent of days in both subgroups of the intervention group, and this percentage did not differ according to the sedative agent used. In addition, there were no differences in the duration of mechanical ventilation or the length of stay in the intensive care unit when patients were grouped according to the sedative they received.

One drawback to continuous intravenous sedation is impaired mental status,[8,25] which may prevent the early detection of neurologic dysfunction resulting from new insults. Stopping the sedative infusion for a period during each day is a simple way to improve clinicians' ability to perform daily neurologic examinations. In our study, most of the diagnostic tests performed to assess changes in mental status were not helpful, but fewer of these tests were performed in the group in which the sedative infusion was interrupted each day than in the control group. Avoiding unnecessary diagnostic studies may reduce the rate of complications related to the transport of patients[26,27] and may reduce costs.

The incidence of adverse events, such as removal of the endotracheal tube by the patient, was low and did not differ significantly between the intervention group and the control group. Because such events were uncommon, the power of this study to detect a difference between the groups may not have been adequate. Nevertheless, the 5 percent overall rate at which patients removed the endotracheal tube compares favorably with the rates of 10 to 12 percent observed in previous studies.[28,29] It is noteworthy that in no case did a patient in the intervention group remove his or her endotracheal tube during an interruption period. There were no differences between the groups in the proportions of patients who needed paralytic drugs, noninvasive ventilation, tracheostomy, reintubation, or transfer to another facility for long-term ventilation, or in the proportion from whom care was withdrawn. The percentage of patients successfully discharged to their homes was greater in the group assigned to daily interruption of infusions than in the control group.

This study has several limitations. We cannot be certain that the clinicians involved in patient care were completely unaware of the study-group assignments. We attempted to minimize this problem by not disclosing the end points of the study to the clinicians. In the case of some patients in the control group, the sedative infusions were periodically interrupted by the intensive care unit team. This practice may have interfered with the detection of differences in outcome between the two groups, since some patients in the control group thus received the potentially beneficial intervention. This study involved patients receiving medical intensive care; whether our results can be extrapolated to other groups of critically ill patients (e.g., those receiving intensive care after surgery or trauma) is not clear. In addition, we monitored visible signs of physical discomfort during interruptions of the sedative infusions. Whether less obvious types of discomfort or psychological distress were present during the daily interruptions of the sedative infusions cannot be discerned from this study.

In conclusion, daily interruption of the infusion of sedative drugs is a safe and practical approach to treating patients who are receiving mechanical ventilation. This practice decreases the duration of mechanical ventilation, the length of stay in the intensive care unit, and the doses of benzodiazepines used. It also improves the ability of clinicians to perform daily neurologic examinations and reduces the need for diagnostic studies to evaluate unexplained alterations in mental status.

We are indebted to the nurses in the medical intensive care unit at the University of Chicago for helping to make this study possible.

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Mechanical Ventilation

Medical Progress

ADVANCES IN MECHANICAL VENTILATION

MARTIN J. TOBIN, M.D.

THE chief reason that patients are admitted to an intensive care unit is to receive ventilatory support. In this article, I update the basic principles of mechanical ventilation, which I reviewed in the *Journal* in 1994,[1] and discuss recent advances.

BASIC PRINCIPLES

The indications for mechanical ventilation, as derived from a study of 1638 patients in eight countries,[2] are acute respiratory failure (66 percent of patients), coma (15 percent), acute exacerbation of chronic obstructive pulmonary disease (13 percent), and neuromuscular disorders (5 percent). The disorders in the first group include the acute respiratory distress syndrome, heart failure, pneumonia, sepsis, complications of surgery, and trauma (with each subgroup accounting for about 8 to 11 percent of the overall group). The objectives of mechanical ventilation are primarily to decrease the work of breathing and reverse life-threatening hypoxemia or acute progressive respiratory acidosis.

Virtually all patients who receive ventilatory support undergo assist-control ventilation, intermittent mandatory ventilation, or pressure-support ventilation; the latter two modes are often used simultaneously.[2] With assist-control ventilation, the most widely used mode, the ventilator delivers a set tidal volume when triggered by the patient's inspiratory effort or independently, if such an effort does not occur within a preselected time.

Intermittent mandatory ventilation was introduced to provide graded levels of assistance. With this mode, the physician sets the number of mandatory breaths of fixed volume to be delivered by the ventilator; between these breaths, the patient can breathe spontaneously.[3] Patients often have difficulty adapting to the intermittent nature of ventilatory assistance, and the decrease in the work of breathing may be much less than desired.[4]

From the Division of Pulmonary and Critical Care Medicine, Edward Hines, Jr., Veterans Affairs Hospital and Loyola University of Chicago Stritch School of Medicine, Hines, Ill. Address reprint requests to Dr. Tobin at the Division of Pulmonary and Critical Care Medicine, Edward Hines, Jr., Veterans Affairs Hospital, Rte. 111N, Hines, IL 60141, or at mtobin2@lmc.edu.

Pressure-support ventilation also provides graded assistance but differs from the other two modes in that the physician sets the level of pressure (rather than the volume) to augment every spontaneous respiratory effort.[5] The level of pressure delivered by the ventilator is usually adjusted in accordance with changes in the patient's respiratory frequency. However, the frequency that signals a satisfactory level of respiratory-muscle rest has never been well defined, and recommendations range from 16 to 30 breaths per minute.[6]

New modes of mechanical ventilation are often introduced. Each has an acronym, and the jargon is inhibiting to those unfamiliar with it. Yet each new mode involves nothing more than a modification of the manner in which positive pressure is delivered to the airway and of the interplay between mechanical assistance and the patient's respiratory effort. The purpose of a new mode of ventilation may be to enhance respiratory-muscle rest, prevent deconditioning, improve gas exchange, prevent lung damage, enhance the coordination between ventilatory assistance and the patient's respiratory efforts, and foster lung healing; the priority given to each goal varies.

COORDINATING RESPIRATORY EFFORT AND MECHANICAL VENTILATION

Probably the most common reason for instituting mechanical ventilation is to decrease the work of the respiratory muscles. The inspiratory effort expended by patients with acute respiratory failure is about four times the normal value, and it can be increased to six times the normal value in individual patients.[7] Critically ill patients in whom this increased level of effort is sustained indefinitely are at risk of inspiratory-muscle fatigue, which can add structural injury to already overworked muscles.[8] It is sometimes thought that the simple act of connecting a patient to a ventilator will decrease respiratory effort. Yet unless the settings are carefully selected, mechanical ventilation can actually do the opposite.

With careful selection of ventilator settings, inspiratory effort can be reduced to the normal range.[9] But eliminating inspiratory effort is not desirable because it causes deconditioning and atrophy of the respiratory muscles.[10] Surprisingly, researchers have not attempted to determine the desirable target for reducing inspiratory effort in patients with acute respiratory distress. To reduce effort markedly requires that the ventilator cycle in unison with the patient's central respiratory rhythm (Fig. 1). For perfect synchronization, the period of mechanical inflation must match the period of neural inspiratory time (the duration of inspiratory effort), and the period of mechanical

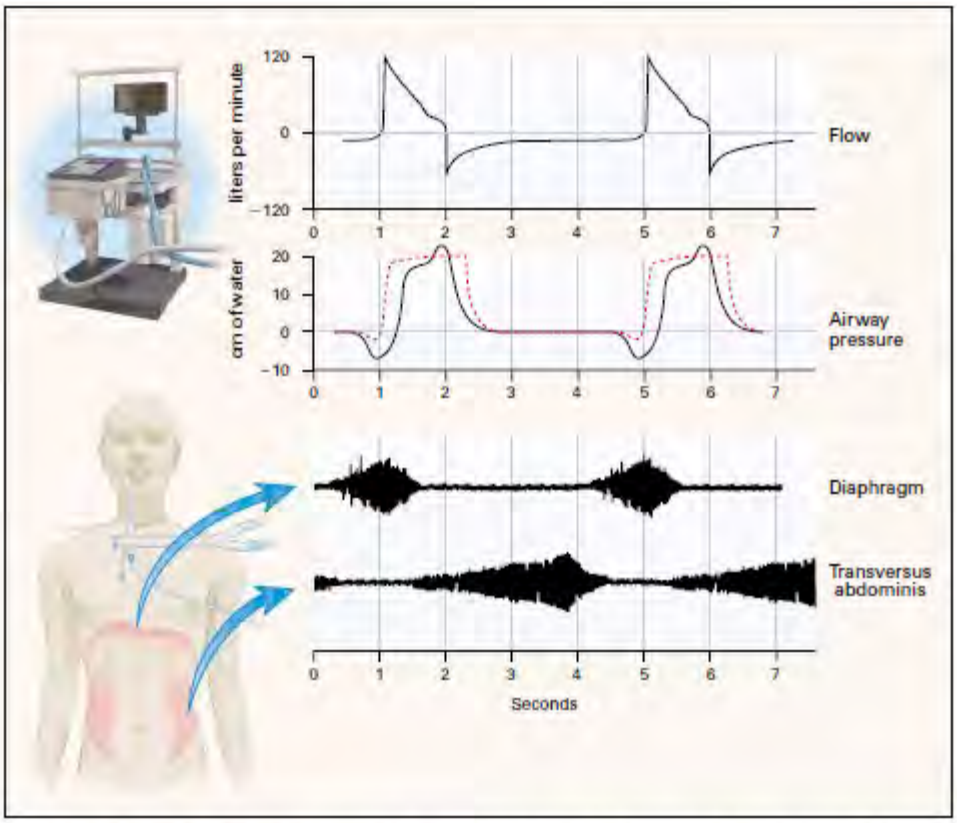

Figure 1. Flow, Airway Pressure, and Inspiratory and Expiratory Muscle Activity in a Patient with Chronic Obstructive Pulmonary Disease Who Received Pressure-Support Ventilation at an Airway Pressure of 20 cm of Water.

The electromyograms in the lower portion of the figure show inspiratory muscle activity in the patient's diaphragm and expiratory muscle activity in the transversus abdominis. The patient's increased inspiratory effort caused the airway pressure to fall below the set sensitivity (−2 cm of water), and inadequate delivery of flow by the ventilator resulted in a scooped contour on the airway-pressure curve during inspiration. While the ventilator was still pumping gas into the patient, his expiratory muscles were recruited, causing a bump in the airway-pressure curve. That the flow never returned to zero throughout expiration reflected the presence of auto–positive end-expiratory pressure. The broken red line shows airway pressure in another patient, who generated just enough effort to trigger the ventilator and in whom there was adequate delivery of gas by the ventilator. Data are from Jubran et al.[6] and Parthasarathy et al.[11]

on ventilator screens has increased awareness that inspiratory effort is frequently insufficient to trigger the ventilator. At high levels of mechanical assistance, up to one third of a patient's inspiratory efforts may fail to trigger the machine.[8,16,17] Surprisingly, unsuccessful triggering is not the result of poor inspiratory effort; indeed, the effort is more than a third greater when the threshold for triggering the ventilator is not reached than when it is reached.[9] Breaths that do not reach the threshold for triggering the ventilator have higher tidal volumes and shorter expiratory times than do breaths that do trigger the ventilator. Consequently, elastic-recoil pressure builds up within the thorax in the form of intrinsic positive end-expiratory pressure (PEEP), or auto-PEEP.[9] To trigger the ventilator, the patient's inspiratory effort first has to generate a negative intrathoracic pressure in order to counterbalance the elastic recoil and then must reach the set sensitivity. The consequences of wasted inspiratory efforts are not fully known, but they add an unnecessary burden in patients whose inspiratory muscles are already under stress.

The inspiratory flow rate is initially set at a default value, such as 60 liters per minute. If the delivered flow does not meet the patient's ventilatory needs, inspiratory effort will increase.[16] Sometimes the flow is increased in order to shorten the inspiratory time and increase the expiratory time, especially in patients with inspiratory efforts that are insufficient to trigger the ventilator. But an increase in flow causes immediate and persistent tachypnea, and as a result, the expiratory time may be shortened.[18] In one study, for example, increases in inspiratory flow from 30 liters per minute to 60 and 90 liters per minute caused increases in the respiratory rate of 20 and 41 percent, respectively.[19]

In studies of interactions between the patient's respiratory efforts and mechanical ventilation, remarkably little attention has been paid to the switch between inspiration and expiration. With the use of pressure-support ventilation, ventilatory assistance ceases when the patient's inspiratory flow falls by a preset amount (e.g., to 25 percent of the peak flow).[5] Air flow changes more slowly in patients with chronic obstructive pulmonary disease than in other patients, and patients often start to exhale while the ventilator is still pumping gas into their chests.[9,11] In 5 of 12 patients with chronic obstructive pulmonary disease who were receiving pressure support of 20 cm of water, expiratory muscles were recruited during ventilator-induced inflation.[9]

IMPROVING OXYGENATION AND PREVENTING LUNG INJURY

A primary goal of mechanical ventilation is to improve arterial oxygenation. Improvement is achieved partly through the use of endotracheal intubation to ensure the delivery of oxygen to the airway and partly through an increase in airway pressure. Satisfactory oxygenation is easily achieved in most patients with airway obstruction. The main challenge arises in patients with alveolar-filling disorders, especially the acute respiratory distress syndrome — a form of noncardiogenic pulmonary edema resulting from severe acute alveolar injury. It has long been recognized that arterial oxygenation can be achieved at a lower inspired oxygen concentration by increasing airway pressure. The goal of using the lowest possible oxygen concentration to achieve an arterial oxygen saturation of approximately 90 percent has not changed in decades. What has changed is how this goal is viewed in relation to other factors, particularly ventilator pressures. In recent years, there has been a growing tendency to be more concerned about high airway pressures than about oxygen toxicity, although this shift has been based on a consensus of opinion rather than on data from studies in patients and animals.

From the outset, clinicians recognized that mechanical ventilation could rupture alveoli and cause air leaks.[20] In 1974, Webb and Tierney showed that mechanical ventilation could also cause ultrastructural injury, independently of air leaks.[21] Their observations went largely unnoticed until a decade later, when several investigators confirmed and extended them. Alveolar overdistention causes changes in epithelial and endothelial permeability, alveolar hemorrhage, and hyaline-membrane formation in laboratory animals.[22]

Diffuse infiltrates on chest radiographs originally led clinicians to infer that lung involvement was homogeneous. But computed tomography (CT) reveals a patchy pattern: about one third of the lung is unaerated, one third poorly aerated, and one third normally aerated.[23,24] A ventilator-induced breath will follow the path of least impediment, travelling preferentially to the normally aerated areas. As a result, these regions are vulnerable to alveolar overdistension and the type of ventilator-induced lung injury found in laboratory animals[25] (Fig. 2).

A new era of ventilatory management began in 1990, when Hickling et al.[26] reported that lowering the tidal volume caused a 60 percent decrease in the expected mortality rate among patients with the acute respiratory distress syndrome. In a subsequent trial, Amato et al.[27,28] randomly assigned patients to a conventional tidal volume (12 ml per kilogram of body weight) or to a low tidal volume (less than 6 ml per kilogram). Mortality was decreased by 46 percent with the lower tidal volume. In a recent study of 861 patients, the Acute Respiratory Distress Syndrome Network[29] confirmed this benefit: mortality was decreased by 22 percent with a tidal volume of 6 ml per kilogram as compared with a tidal volume of 12 ml per kilogram. Lowering the tidal volume, however, failed to improve the outcome in three controlled trials.[30-32] The discrepant findings can be explained by differences in trial design. Increased survival was de-

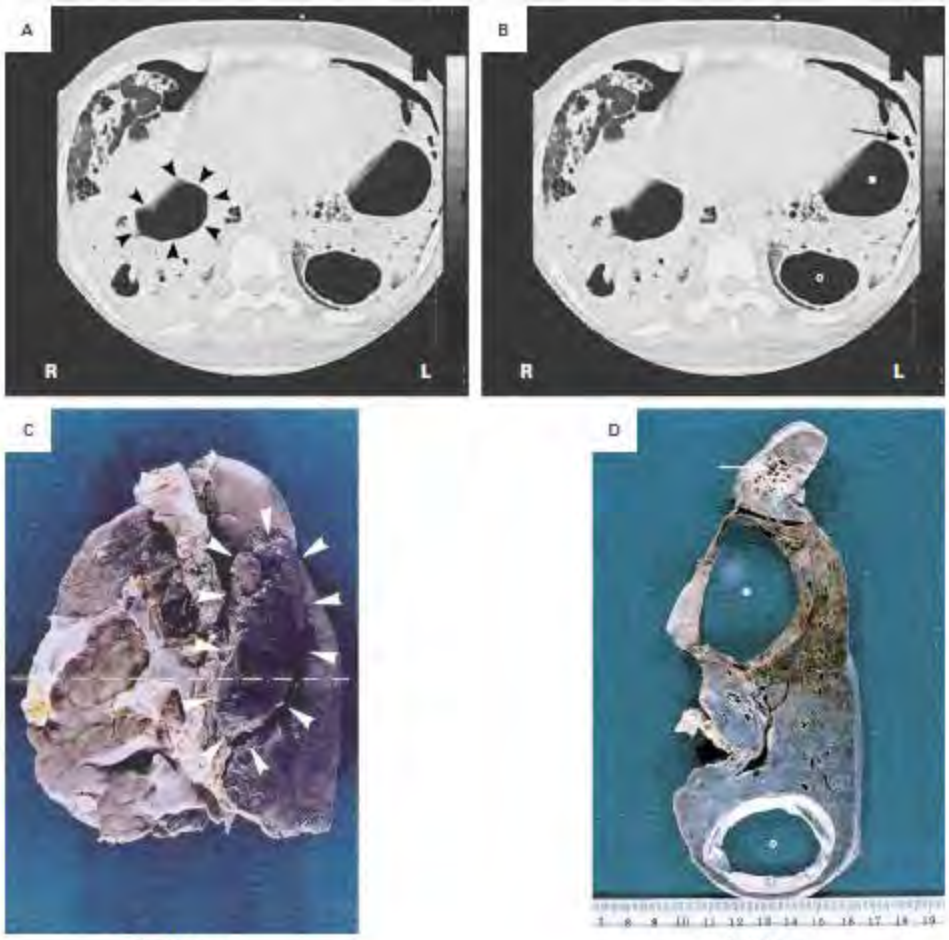

Figure 2. Lung Injury Caused by Mechanical Ventilation in a 31-Year-Old Woman with the Acute Respiratory Distress Syndrome Due to Amniotic-Fluid Embolism.

The patient had undergone mechanical ventilation for eight weeks with tidal volumes of 12 to 15 ml per kilogram of body weight, peak airway pressures of 50 to 70 cm of water, positive end-expiratory pressures of 10 to 15 cm of water, and a fractional inspired oxygen concentration of 0.80 to 1.00 in order to achieve a partial pressure of carbon dioxide that was less than 50 mm Hg and a partial pressure of oxygen that was 80 mm Hg or higher. Computed tomography (CT) performed two days before the patient died revealed a paramediastinal pneumatocele in the right lung (Panel A, arrowheads) and numerous intraparenchymal pseudocysts in the left lung (Panel B, black arrow, open circle, and asterisk).

At autopsy, both lungs were removed and fixed by intrabronchial infusion of formalin, alcohol, and polyethylene glycol at an insufflation pressure of 30 cm of water. Panel C shows the paramediastinal pneumatocele in the right lung (arrowheads); the horizontal broken line is the level of the CT section. Panel D shows a 1-cm-thick section of the left lung, corresponding to the CT section. Small pseudocysts are present (arrow), and two large pseudocysts (asterisk and open circle) have compressed and partially destroyed the parenchyma. The development of these lesions in a patient without a history of chronic lung disease indicates the harm that may result with the use of high tidal volumes and airway pressures. The photographs were kindly provided by Dr. Jean-Jacques

monstrable only when the patients undergoing conventional ventilation had a mean pressure during an end-inspiratory pause (the so-called plateau pressure, a surrogate for peak alveolar pressure) that exceeded 32 cm of water.[33]

The pressures pertinent to ventilatory management are the peak inspiratory pressure, plateau pressure, and end-expiratory pressure. Patients with airway obstruction may have a very high peak pressure without any increase in the plateau pressure. Indeed, the gradient between the two is directly related to the resistance of the airway to airflow. An increase in the peak inspiratory pressure without a concomitant increase in the plateau pressure is unlikely to cause alveolar damage. The critical variable is not airway pressure itself but transpulmonary pressure — airway pressure during the end-inspiratory pause minus pleural pressure. The normal lung is maximally distended at a transpulmonary pressure between 30 and 35 cm of water, and higher pressures cause overdistention. Patients with stiff chest walls, such as those with the acute respiratory distress syndrome due to a nonpulmonary disorder (e.g., abdominal sepsis), have an elevated pleural pressure. In such patients, the airway plateau pressure may exceed 35 cm of water without causing alveolar overdistention.

Clinical decisions based on plateau pressure must take into account the relation between lung volume and airway pressure in the individual patient. The pressure–volume curve in patients with the acute respiratory distress syndrome typically has a sigmoid shape with two discrete bends, called inflection points (Fig. 3).[34] Some investigators believe that a plateau pressure above the upper bend causes alveolar overdistention. Reducing the tidal volume lowers the plateau pressure, but at the cost of hypercapnia. In a study in which 25 patients with the acute respiratory distress syndrome underwent mechanical ventilation with a tidal volume of 10 ml per kilogram, 20 had a plateau pressure that was 2 to 14 cm of water above the upper bend of the pressure–volume curve.[35] Lowering the plateau pressure to a value that fell below the upper bend required a 22 percent decrease in the tidal volume, causing the partial pressure of carbon dioxide to increase from 44 to 77 mm Hg.[35] The partial pressure of carbon dioxide, in turn, can be decreased by as much as 28 percent by removing tubing and thus decreasing dead space and increasing the frequency of ventilator-induced breaths. By virtue of their stiff lungs, patients with the acute respiratory distress syndrome who do not have an underlying airway obstruction can tolerate a frequency of 30 breaths per minute without gas trapping.[36] Severe hypercapnia can have adverse effects, including increased intracranial pressure, depressed myocardial contractility, pulmonary hypertension, and depressed renal blood flow.[37,38] The view that these risks are preferable to the higher plateau pressure required to achieve normocapnia represents a substantial shift in ventilatory management.

Lowering the tidal volume is not without hazards. In addition to the potential harm of hypercapnia, the volume of aerated lung may be decreased,[39] with a consequent increase in shunting and worsening oxygenation. One means of minimizing the loss of lung volume is the use of sighs (i.e., single breaths of large tidal volume). In one study, increasing the plateau pressure by at least 10 cm of water during sighs, applied three times a minute over a period of one hour, caused a 26 percent decrease in shunting, with a 50 percent increase in the partial pressure of oxygen.[40] It is unknown whether sighs used at this low frequency cause injury from alveolar overdistention.

The more usual way of improving oxygenation is through the use of PEEP with the intention of recruiting previously nonfunctioning lung tissue. Selecting the right level of PEEP for a given patient with the acute respiratory distress syndrome is difficult, because the severity of injury varies throughout the lungs. PEEP can recruit atelectatic areas but may overdistend normally aerated areas.[41,42] In a study involving six patients with acute lung injury, for example, the use of PEEP at 13 cm of water resulted in the recruitment of nonaerated portions of lung, with a gain of 320 ml in volume, but three patients had overdistention of already aerated portions of lung, with an excess volume of 238 ml.[43]

Overall, about 30 percent of patients with acute lung injury do not benefit from PEEP or have a fall in the partial pressure of oxygen.[32,44,45] With the patient in the supine posture, PEEP generally recruits the regions of the lung closest to the apex and sternum.[23] Conversely, PEEP can increase the amount of nonaerated tissue in the regions close to the spine and the diaphragm.[23] Among patients in the early stages of the acute respiratory distress syndrome, those with pulmonary causes, such as pneumonia, are less likely to benefit from PEEP than are those with nonpulmonary causes, such as intraabdominal sepsis or extrathoracic trauma.[46] This distinction may be related to the type of morphologic involvement: pulmonary causes of the syndrome are characterized by alveolar filling, whereas nonpulmonary causes are characterized by interstitial edema and alveolar collapse. In the later stages of the acute respiratory distress syndrome, remodeling and fibrosis may eliminate this distinction between pulmonary and nonpulmonary causes.

To select the right level of PEEP, some experts recommend bedside calculation of the pressure–volume curve. With the ventilators currently used in the United States, calculating the pressure–volume curve is logistically difficult and technically demanding.[34] Yet many ventilators have a computer screen, and minor software modifications would make it feasible to calculate the curve in as little as two minutes — as with the ventilators available in France.[47] Providing

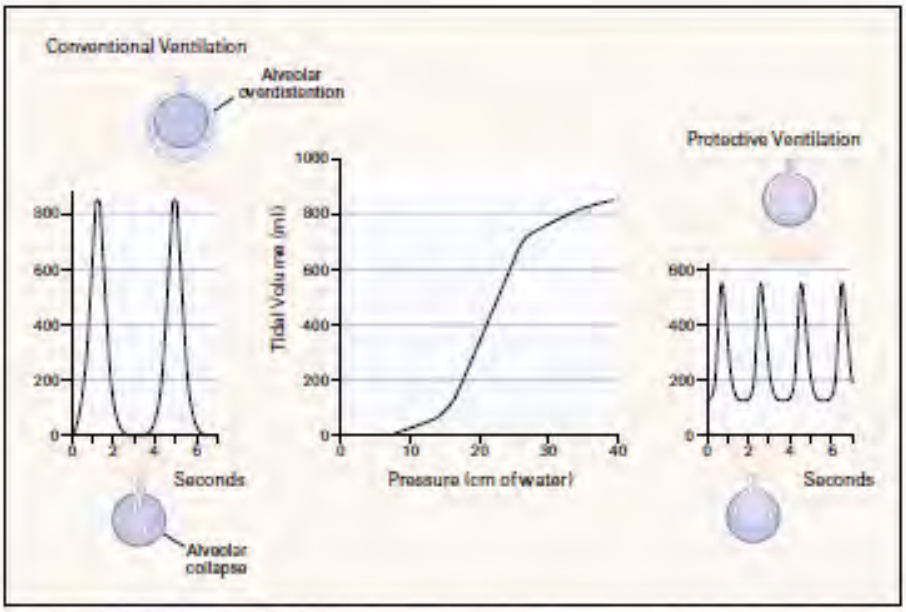

Figure 3. Respiratory Pressure–Volume Curve and the Effects of Traditional as Compared with Protective Ventilation in a 70-kg Patient with the Acute Respiratory Distress Syndrome.

The lower and upper inflection points of the inspiratory pressure–volume curve (center panel) are at 14 and 26 cm of water, respectively. With conventional ventilation at a tidal volume of 12 ml per kilogram of body weight and zero end-expiratory pressure (left-hand panel), alveoli collapse at the end of expiration. The generation of shear forces during the subsequent mechanical inflation may tear the alveolar lining, and attaining an end-inspiratory volume higher than the upper inflection point causes alveolar overdistention. With protective ventilation at a tidal volume of 6 ml per kilogram (right-hand panel), the end-inspiratory volume remains below the upper inflection point; the addition of positive end-expiratory pressure at 2 cm of water above the lower inflection point may prevent alveolar collapse at the end of expiration and provide protection against the development of shear forces during mechanical inflation.

this option on ventilators would increase clinicians' experience with the use of pressure–volume curves in ventilatory management.

Even if the pressure–volume curve is not calculated at the bedside, it is useful to select the PEEP level according to this conceptual framework. A level above the lower bend in the pressure–volume curve is thought to keep alveoli open at the end of expiration and thus prevent the injury that can result from shear forces created by the opening and closing of alveoli.[48,63] This level of PEEP may also prevent an increase in the amount of nonaerated tissue and, thus, atelectasis. However, the notion that the lower bend signals the level of PEEP necessary to prevent end-expiratory collapse and that pressures above the upper bend signal alveolar overdistention is a gross oversimplification. The relation between the shape of the pressure–volume curve and events at the alveolar level is confounded by numerous factors and is the subject of ongoing research and debate.[61-65] An understanding of this relation is also impeded by the difficulty in distinguishing collapsed lung units from fluid-filled units on CT.

Most patients with the acute respiratory distress syndrome have an increase in the partial pressure of oxygen when there is a change from the supine to the prone position. In a study of 16 patients, for example, 12 had an increase of 9 to 73 mm Hg in the partial pressure of oxygen, and 4 had a decrease of 7 to 16 mm Hg.[66] The mechanism responsible for the improvement in the partial pressure of oxygen is not clear. The attribution of this improvement to lung recruitment has not been proved.[65] It is now posited that a prone position causes ventilation to be distrib-

ated more evenly to the various regions of the lungs,[57,58] improving the relation between ventilation and perfusion.[59,60]

DISCONTINUING MECHANICAL VENTILATION

Because mechanical ventilation can have life-threatening complications, it should be discontinued at the earliest possible time. The process of discontinuing mechanical ventilation, termed weaning, is one of the most challenging problems in intensive care, and it accounts for a considerable proportion of the workload of staff in an intensive care unit.[2]

When mechanical ventilation is discontinued, up to 25 percent of patients have respiratory distress severe enough to necessitate the reinstitution of ventilatory support.[61,62] Our understanding of why weaning fails in some patients has advanced considerably in recent years. Among patients who cannot be weaned, disconnection from the ventilator is followed almost immediately by an increase in respiratory frequency and a fall in tidal volume — that is, rapid, shallow breathing[63] (Fig. 4). As a trial of spontaneous breathing is continued over the next 30 to 60 minutes, the respiratory effort increases considerably, reaching more than four times the normal value at the end of this period.[7] The increased effort is mainly due to worsening respiratory mechanics. Respiratory resistance increases progressively over the course of a trial of spontaneous breathing, reaching about seven times the normal value at the end of the trial; lung stiffness also increases, reaching five times the normal value; and gas trapping, measured as auto-PEEP, more than doubles over the course of the trial.[7] Before weaning is started, however, the respiratory mechanics in such patients are similar to those in whom subsequent weaning is successful.[64] Thus, unknown mechanisms associated with the act of spontaneous breathing cause the worsening of respiratory mechanics in patients who cannot be weaned from mechanical ventilation.

In addition to the increase in respiratory effort, an unsuccessful attempt at spontaneous breathing causes considerable cardiovascular stress.[65] Patients can have substantial increases in right and left ventricular afterload, with increases of 39 and 27 percent in pulmonary and systemic arterial pressures, respectively,[64] most likely because the negative swings in intrathoracic pressure are more extreme. At the completion of a trial of weaning, the level of oxygen consumption is equivalent in patients who can be weaned and in those who cannot. But how the cardiovascular system meets the oxygen demand differs in the two groups of patients.[64] In those who are successfully weaned, the oxygen demand is met through an increase in oxygen delivery, mediated by the expected increase in cardiac output on discontinuation of positive-pressure ventilation. In patients who cannot be weaned, the oxygen demand is met through an increase in oxygen extraction, and these patients have a relative decrease in oxygen delivery.[64] The greater oxygen extraction causes a substantial decrease in mixed venous oxygen saturation, contributing to the arterial hypotemia that occurs in some patients.[66]

Over the course of a trial of spontaneous breathing, about half of patients in whom the trial fails have an increase in carbon dioxide tension of 10 mm Hg or more.[7] The hypercapnia is not usually a consequence of a decrease in minute ventilation.[63] Instead, hypercapnia results from rapid, shallow breathing, which causes an increase in dead-space ventilation. In a small proportion of patients who cannot be weaned, primary depression of respiratory drive may be responsible for the hypercapnia.[7]

The discontinuation of mechanical ventilation needs to be carefully timed. Premature discontinuation places severe stress on the respiratory and cardiovascular systems, which can impede the patient's recovery. Unnecessary delays in discontinuation can lead to a host of complications. Decisions about timing that are based solely on expert clinical judgment are frequently erroneous.[67-70] Several functional measures are used to aid decision making. The level of oxygenation must be satisfactory before one attempts to discontinue mechanical ventilation. Yet in many patients with satisfactory oxygenation, such attempts fail. The use of traditional predictors of the success or failure of attempts — maximal inspiratory pressure, vital capacity, and minute ventilation — frequently has false positive or false negative results.[71] A more reliable predictor is the ratio of respiratory frequency to tidal volume (f/V_T).[72] The ratio must be calculated during spontaneous breathing; calculating it during pressure support markedly impairs its predictive accuracy.[68] The higher the ratio, the more severe the rapid, shallow breathing and the greater the likelihood of unsuccessful weaning. A ratio of 100 best discriminates between successful and unsuccessful attempts at weaning. In a case of clinical equipoise — that is, a pretest probability of 50 percent — an f/V_T of 80, which has a likelihood ratio of 7.5, is associated with almost a 95 percent post-test probability of successful weaning.[73] If the f/V_T is higher than 100, the likelihood ratio is 0.04 and the post-test probability of successful weaning is less than 5 percent.

Several groups of investigators have evaluated the predictive value of f/V_T.[74-78] Its positive predictive value — the proportion of patients who are successfully weaned among those for whom the ratio predicts success — has generally been high (0.8 or higher). The negative predictive value — the proportion of patients who cannot be weaned among those for whom the ratio predicts failure — has sometimes been reported to be low (0.5 or less). Low negative predictive values have often been reported for patients with a high likelihood of successful extubation — for example, patients undergoing routine postop-

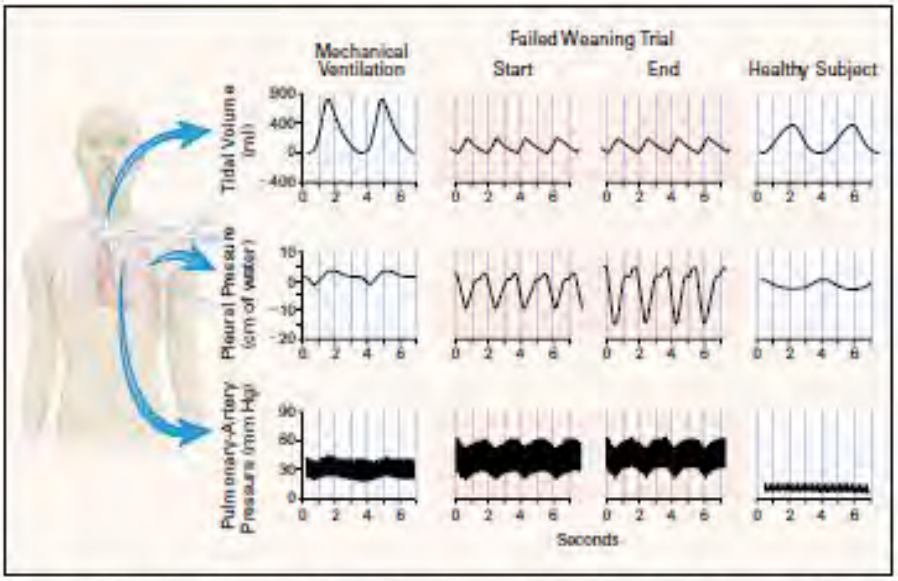

Figure 4. Tidal Volume, Pleural Pressure, and Pulmonary-Artery Pressure in a Patient Undergoing Assist-Control Ventilation and at the Start and End of a Failed Trial of Spontaneous Breathing.

During mechanical ventilation, the patient's inspiratory effort is in the normal range and the pulmonary-artery pressure is 49/22 mm Hg (systolic/diastolic). At the start of the trial of spontaneous breathing, the tidal volume falls to 200 ml, the respiratory frequency increases to 33 breaths per minute, there are swings in pleural pressure of 11 cm of water, and the pulmonary-artery pressure at the end of expiration is 60/28 mm Hg. At the end of the trial, 45 minutes later, the tidal volume and respiratory frequency are unchanged, there are swings in pleural pressure of 19 cm of water, auto-positive end-expiratory pressure is 4 cm of water, and the pulmonary-artery pressure is 60/31 mm Hg. The values in a healthy subject are tidal volume, 380 ml; respiratory frequency, 17 breaths per minute; pleural-pressure swings, 3 cm of water; and pulmonary-artery pressure, 18/8 mm Hg. Data are from Tobin et al.[4,46] and Jubran et al.[76]

erative ventilatory assistance and patients who have tolerated initial trials of weaning.[75,76]

There are four methods of weaning.[79] The oldest method is to perform trials of spontaneous breathing several times a day, with the use of a T-tube circuit containing an enriched supply of oxygen. Initially 5 to 10 minutes in duration, the trials are extended and repeated several times a day until the patient can sustain spontaneous ventilation for several hours. This approach has become unpopular because it requires considerable time on the part of intensive care staff.

The two most common approaches, intermittent mandatory ventilation and pressure support, decrease ventilatory assistance gradually by respectively lowering the number of ventilator-assisted breaths or the level of pressure. When a minimal level of ventilatory assistance can be tolerated, the patient is extubated. The minimal level of assistance, however, has never been well defined. For example, pressure support of 6 to 8 cm of water is widely used to compensate for the resistance imposed by the endotracheal tube and ventilator circuit.[80] A patient who can breathe comfortably at this level of pressure support should be able to tolerate extubation. But if the upper airways are swollen because an endotracheal tube has been in place for several days, the work engendered by breathing through the swollen airways is about the same as that caused by breathing through an endotracheal tube.[81] Accordingly, any amount of pressure support overcompensates and may give misleading information about the likelihood that a patient can tolerate extubation.

The fourth method of weaning is to perform a single daily T-tube trial, lasting for up to two hours. If this trial is successful, the patient is extubated; if the trial is unsuccessful, the patient is given at least

24 hours of respiratory-muscle rest with full ventilatory support before another trial is performed.[42]

Until the early 1990s, it was widely believed that all weaning methods were equally effective, and the physician's judgment was regarded as the critical determinant. But the results of randomized, controlled trials clearly indicate that the period of weaning is as much as three times as long with intermittent mandatory ventilation as with trials of spontaneous breathing.[43,52] In a study involving patients with respiratory difficulties on weaning, trials of spontaneous breathing halved the weaning time as compared with pressure support[52]; in another study, the weaning time was similar with the two methods.[43] Performing trials of spontaneous breathing once a day is as effective as performing such trials several times a day[52] but much simpler. In a recent study, half-hour trials of spontaneous breathing were as effective as two-hour trials.[43] However, this study involved all patients being considered for weaning, not just those for whom there were difficulties with weaning.

A two-stage approach to weaning — systematic measurement of predictors, including f/V_T, followed by a single daily trial of spontaneous breathing — was compared with conventional management in a randomized trial.[46] Although the patients assigned to the two-stage approach were sicker than those assigned to conventional weaning, they were weaned twice as rapidly. The rate of complications and the costs of intensive care were also lower with two-stage management than with conventional management.

When patients can sustain spontaneous ventilation without undue discomfort, they are extubated. About 10 to 20 percent of such patients require reintubation.[43,53] Mortality among patients who require reintubation is more than six times as high as mortality among patients who can tolerate extubation.[53,54] The reason for the higher mortality is unknown; it is not clearly related to the development of new problems after extubation or to complications of reinserting the tube. Indeed, the need for reintubation may simply be a marker of a more severe underlying illness.

In a controlled trial involving patients who could not sustain spontaneous ventilation, the patients who were extubated and then received noninvasive ventilation through a face mask had a shorter mean overall period of ventilatory support (10.2 days) than those who remained intubated and were weaned by decreasing pressure support (16.6 days).[46] Although this result is promising, it is not clear how many such patients or which ones could benefit from this approach.

OTHER APPROACHES TO MECHANICAL VENTILATION

Noninvasive ventilation, an approach that is becoming more widespread, was reviewed in the *Journal* in 1997.[55] Two new approaches under investigation are liquid ventilation[57] and proportional-assist ventilation[58]; they have not yet been approved for general clinical use.

CONCLUSIONS

Since my previous overview of mechanical ventilation in the *Journal*, we have gained a better understanding of the pathophysiology associated with unsuccessful weaning and have learned how to wean patients more efficiently. We have also learned how ventilator settings influence survival in patients with the acute respiratory distress syndrome. Less progress has been made in determining how the ventilator can best be used to achieve maximal respiratory-muscle rest, which is the most common reason for providing mechanical ventilation. Although further research may lead to unexpected new insights, an important challenge for researchers is to identify elements of our current knowledge that can be incorporated into a clinical management scheme to improve the outcome for patients who require ventilatory assistance.

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Mechanical Ventilators in Critically ill Patients: Physiologic Principle and Ventilatory Strategies

Harakh V. Dedhia, M.D.
Section Of Pulmonary - CCM
Director, MICU and Respiratory Care
WVU Health Sciences Center
Morgantown, West Virginia

Mechanical Ventilators: What will be covered?

- Indication and Goals Ventilators
- How to initiate ventilator
- Use of ventilators in obstructive airway disease and ARDS
- Side effects of ventilators
- How to wean patient from a ventilator
- Evaluation and management of "patient in distress" while on ventialtor
- Questions / Answers
- Graphics on Ventialtors

Q. 1

A 25 year old, 50 kg woman with a history of asthma experienced severe dyspnea with a respiratory rate of 38/min and mental status changes. Shortly after she intubated oro-tracheally, and started on mechanical ventilation. She became severely hypotensive (60/40 mm Hg). The patient has symmetrical bilaterally decreased breath sounds. Her neck veins are flat.

Q. 1.....

Which **one** of the following is the **most** appropriate next step in managing this patient?

A. Fluid bolus with lactated Ringer's solution
B. Reduce the ventilator rate by 50%
C. Echocardiogram-guided pericardiocentesis
D. Bilaterial chest tubes insertion
E. Flumazenil 0.2 mg IV

Indications for Mechanical Ventilation

- **Ventilation abnormalities**

1. Respiratory muscle dysfunction
   - Respiratory muscle fatigue
   - Chest wall abnormalities
   - Neuromuscular disease
2. Decreased ventilatory drive
3. Increased airway resistance and/or obstruction

Indications for Mechanical Ventilation

- **Oxygenation abnormalities**
  - **Refractory hypoxemia**
  - **Need for positive end-expiratory pressure (PEEP)**
  - **Excessive work of breathing**

Mechanical Ventilation: Goals

- Improve pulmonary gas exchange:
- 1. Reverse hypoxemia ($PaO_2 \geq 70$, on $FiO_2 \leq 0.5$)
- 2. Correct life-threatening acidemia (pH)
- 3. Maintain adequate ventilation ($PaCO_2$)
- Relief from acute respiratory distress: rest for fatigued muscles, Decreased W.O.B.
- Minimal pulmonary barotrauma & cardiovascular impairment: Practical Strategies
- Avoid respiratory muscle atrophy and chronic ventilator dependence

  Patient comfort and synchrony
- Weaning: ASAP and as tolerated
- Avoid oxygen toxicity

Respirator Terminology

- SIMV = Synchronized Intermittent Mandatory Ventilation
- AC = Assist Control
- PC = Pressure Control
- PS = Presser Support
- CPAP = Continuous Positive Pressure Ventilation
- PC = Pressure Control
- IRV = Inverse Ratio Ventilation, Permissive Hypercarbia
- MMV = Mandatory Minute Ventilation

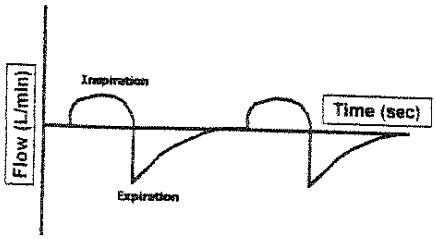
Types of Ventilator Breaths

- Volume-cycled breath
  - "Volume breath"
  - Preset tidal volume
- Time-cycled breath
  - "Pressure control breath"
  - Constant pressure for preset time
- Flow-cycled breath
  - "Pressure support breath"
  - Constant pressure during inspiration

Respirator Terminology II

- TGI = Tracheal Gas insufflation
- IDV = Intermittent Demand Ventilation
- ILV = Independent Lung Ventilation
- PRVC = Pressure Regulated Volume Control
- PAV = Pressure Assist Ventilation
- HFJV = High Frequency Jet Ventilation
- ECMO = Extra Corporeal Membrane Oxygenation
- APRV = Airway Pressure Release Ventilation
- $ECCO_2$ = Extra Corporeal CO_2 removal
- T Piece Trial

Spontaneous Breath



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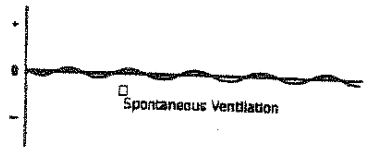
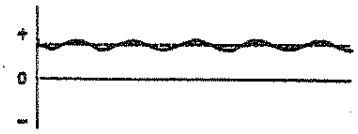
Modes of Mechanical Ventilation

Spontaneous Ventilation

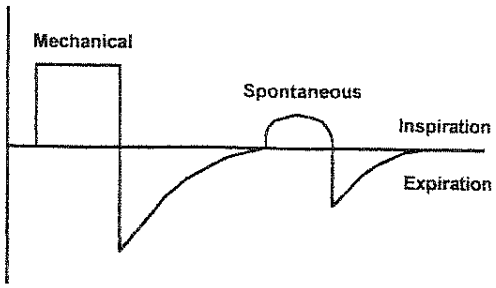


Continuous Positive Airway Pressure (CPAP)

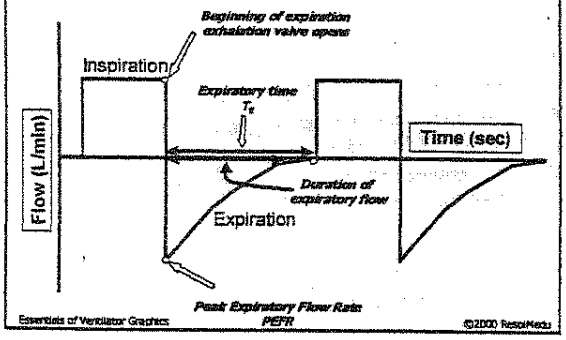
- No machine breaths delivered
- Allows spontaneous breathing at elevated *baseline pressure*
- Patient controls rate and tidal volume



Mechanical vs. Spontaneous

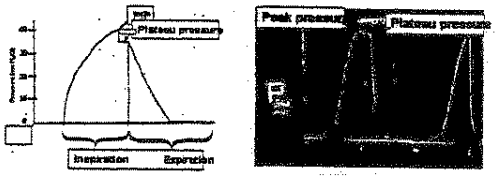


Expiratory Flow Pattern



Inspiratory Plateau Pressure (IPP)

- Airway pressure measured at end of inspiration with no gas flow present
- Estimates alveolar pressure at end-inspiration
- Indirect indicator of alveolar distension



Initiation of Conventional Ventilator

- MODE = SIMV/AC , TV = 8 to 10 ml/ kg (ideal),
- f = 12 to 15, adjust to maintain normal $PaCO_2$
- FiO_2 < 0.5 (may start at a higher value)
- Flow rate = 40 to 60 LPM
- Maintain Paw ≤ 50, Plateau P ≤30 cm water
- I:E ratio 1:2 or greater
- PEEP = 5 cm,
- Set alarms, sensitivity, pressure support 8-10 cm
- Judicious use of sedatives, analgesics & paralytic agents

Inspiratory Peak & Plateau Pressure

- High inspiratory Peak & Plateau pressure associated with
  - Barotrauma
  - Volutrauma
  - Decreased cardiac output
- Methods to decrease IPP
  - Decrease PEEP
  - Decrease tidal volume

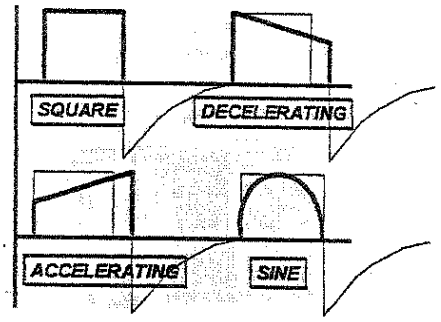
Inspiratory Time: Expiratory Time Relationship (I:E ratio)

- Spontaneous breathing I:E = 1:2
- Inspiratory time determinants with volume breaths
  - Tidal volume
  - Gas flow rate
  - Respiratory rate
  - Inspiratory pause
- Expiratory time passively determined

I:E Ratio during Mechanical Ventilation

- Expiratory time too short for exhalation
  - Breath stacking
  - Auto-PEEP
- Reduce auto-PEEP by shortening inspiratory time
  - Decrease respiratory rate
  - Decrease tidal volume
  - Increase gas flow rate

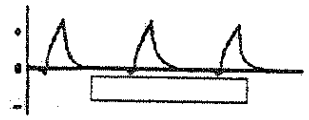
Flow Patterns



Essentials of Ventilator Graphics ©2000 RespiRetu

Assist-Control Ventilation

- Volume or time-cycled breaths + minimal ventilator rate
- Additional breaths delivered with inspiratory effort
- Advantages: reduced work of breathing; allows patient to modify minute ventilation
- Disadvantages: potential adverse hemodynamic effects or inappropriate hyperventilation

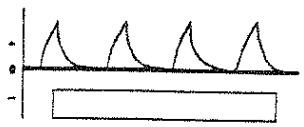


Assist-Control Ventilation

- Volume or time-cycled breaths + minimal ventilator rate
- Additional breaths delivered with inspiratory effort
- Advantages: reduced work of breathing; allows patient to modify minute ventilation
- Disadvantages: potential adverse hemodynamic effects or inappropriate hyperventilation

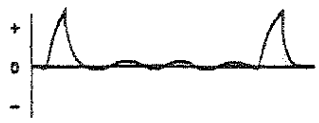
Controlled Mechanical Ventilation

- Preset rate with volume or time-cycled breaths
- No patient interaction with ventilator
- Advantages: rests muscles of respiration
- Disadvantages: requires sedation/neuro-muscular blockade, potential adverse hemodynamic effects



Synchronized Intermittent Mandatory Ventilation (SIMV)

- Volume or time-cycled breaths at a preset rate
- Additional spontaneous breaths at tidal volume and rate determined by patient
- Used with pressure support

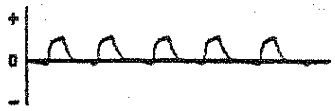


Synchronized Intermittent Mandatory Ventilation (SIMV)

- Potential advantages
  - More comfortable for some patients
  - Less hemodynamic effects
- Potential disadvantages
  - Increased work of breathing

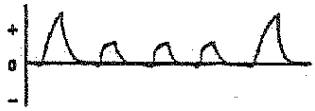
Pressure-Support Ventilation

- Pressure assist during spontaneous inspiration with flow-cycled breath
- Pressure assist continues until inspiratory effort decreases
- Delivered tidal volume dependent on inspiratory effort and resistance/compliance of lung/thorax



Pressure-Support Ventilation

- Potential advantages
  - Patient comfort
  - Decreased work of breathing
  - May enhance patient-ventilator synchrony
  - Used with SIMV to support spontaneous breaths



Pressure-Support Ventilation

- Potential disadvantages
  - Variable tidal volume if pulmonary resistance/compliance changes rapidly
  - If sole mode of ventilation, apnea alarm mode may be only backup
  - Gas leak from circuit may interfere with cycling

Monitoring in patient on a ventilator

- Monitor and record current Fi02
- Pa02 / Fi02 Ratio, Arterial blood gas
- Lung compliance
- End tidal CO2 (P_ECO_2)
- Ventilator alarms: Generally will have high and low alarm for Fi02, tidal volume (exhaled), Minute volume, airway pressures (peak, low, mean +), PEEP, temperature, disconnect

Issues in Mechanical Ventilation

- Different Strategy based on underlying disease
- Ventilator patient aynchrony / Dys - synchrony
- Alveolar distension, Auto PEEP
- Pulmonary barotrauma / (Volutrauma / Stretch)
- Pulmonary infection : VAP
- Inflammatory cytokines release
- Cardiovascular Impairment and Diminished hepatic, renal & splanchnic blood flow (MODS)
- Respiratory Muscle Fatigue / weakness
- Fluid retention: ADH effect
- Elevation in ICP

Q.4

A patient with severe pulmonary disease (COPD) is admitted to the ICU with acute hypercapnic respiratory failure requiring ventilatory support. The patient's respiratory rate is 26 breaths/min. He is started on a mechanical ventilator.

Q.4 contd.

Which ***one*** of the following would ***least*** likely be associated with dynamic hyperinflation in this patient?

A. Inverse-ratio ventilation

B. Pressure-support ventilation

C. Assist-control (volume) ventilation with low inspiratory flow rates

D. Assist-control (volume) ventilation with an end-inspiratory pause

Mechanical Ventilators in Severe airway Obstruction (SAO)

- Can be a life saving
- Increased morbidity & mortality in patients on MV
- Some complications are directly attributed to MV: Mean 13 % (1 to 38%) i.e. Pneumothorax, pneumomediastinum, subcutaneous air, hypotension.

Initiation of Ventilation in SAO

Differences:

F = 10 – 12 / min (low)

- Flow rate 60 to 100 L/min, square wave form
- I:E time 1:3 or 1:4
- FiO_2 as needed, PEEP physiological (2-5 cm)
- Avoid Auto PEEP / Air trapping
- Frequent use of CPAP and PS at higher level

Dynamic Hyperinflation (DHI)

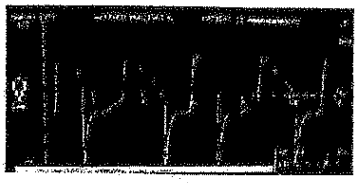
- Very common in Severe Airway Obstruction
- Increase in lung volumes and air trapping
- Elevated Peak and Plateau pressures
- Associated with high incidence of both pulmonary barotrauma & cardiac impairment
- Patients ventilation demand increases (rate, MV, W.O.B., and $PaCO_2$)..... Restless, agitated patient
- Attempt to correct High $PaCO_2$ by increasing rate can worsen DHI

Dynamic Hyperinflation (DHI): Auto PEEP

- Total PEEP = Auto PEEP + Imposed PEEP
- Reflects alveolar pressure at the end of expiration.
- It may not be "0" (higher than imposed PEEP)
- Not readily apparent on a "casual look" at the pressure manometer
- Accurate measurement is essential.
- Patient must be "fully relaxed"
- Monitor flow and pressure graphics, BICORE use

Auto-PEEP

- Can be measured on some ventilators
- Increases peak, plateau, and mean airway pressures
- Potential harmful physiologic effects



Auto-PEEP

- Can be measured on some ventilators
- Increases peak, plateau, and mean airway pressures
- Potential harmful physiologic effects

Permissive Hypercapnia

- Acceptance of an elevated $PaCO_2$, e.g., lower tidal volume to reduce peak airway pressure
- Contraindicated with increased intracranial pressure
- Consider in severe asthma and ARDS
- Critical care consultation advised

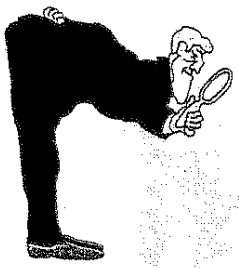
Q.2 A 35 year old man weighing 70 kg is admitted with severe asthma requiring a ventilator. He is sedated and paralyzed, on AC mode with a rate of 15 breaths/min; tidal volume of 1000 ml, and an inspiratory flow rate of 60 L/min, which gives an inspiratory-expiratory (I:E) ratio of 1:3. He is not on any PEEP, and an end-expiratory hold maneuver reveals an auto-PEEP of 15 cm H_2O.

Q. 2 contd.

Which **one** of the following options is likely to be **most** effective in **minimizing** the auto-PEEP?

A. Decreasing the respiratory rate of 12 breaths / min, giving an I:E ratio of 1:4
B. Increasing the flow rate to 120 L/min, giving an I:E ratio of 1:7
C. Decreasing the tidal volume to 900 mL
D. Adding an external PEEP of 5 cm H_2O
E. Changing the square root flow delivery pattern to a decelerating mode

Dynamic Hyperinflation (DHI): Methods of Assessment



- Lung volume measurement at the end of inspiration
- Measurement of Plateau pressure (P plat)
- Auto PEEP

DHI: Affecting Factors

- **INCREASING DHI**
  - *Severe obstruction
  - *Bronchospasm +++, *I:E ratio 1:2 or ≤ .
- *High RR, TV & MV (≥ 15 L).
  - *Low Inspiratory Flow Rate
  - *Agitated, restless patient
- **DECREASING DHI**
  - *Less obstruction
  - *Increased Expiratory time
- *I:E ratio ≥ 1:4
- *Lower RR, TV & MV.
- *High Inspiratory Flow Rate
- *Tranquil, sedated patient

DHI: Management

- Increased Awareness
- Pharmacological: Liberal use of sedatives (decreased drive, W.O.B. &VO_2, decreased VCO_2.
- Aggressive use of bronchodilator.
- Absolute Increase in Expiratory time (Decrease inspiratory time): Lower RR & TV (5-8 ml/kg), Increase Flow Rate
- Controlled Passive Hypercarbia (Lung protective strategy)
- Add External PEEP to reduce W.O.B.

Effect of RR, Flow & TV on I:E time and ratio

RR	Flow rate (L/min)	*TV* (L)	Cycle T (sec)	*Insp.T* (sec)	Exp.T (sec)	I:E ratio
15	60	1	4	1	3	1:3
12	60	1	5	1	4	1:4
12	120	1	5	0.5	4.5	1:9
15	60	0.5	4	0.5	3.5	1:7
20	60	1	3	1	2	1:2
20	120	1	3	0.5	2.5	1:5

Putting Things Together

Obstructive Airway Disease

L.W. is a 62-yr-old, 52-kg female with severe emphysema. For 2 days she has had progressive dyspnea and was found unresponsive. Following this radiograph, she required intubation and initiation of mechanical ventilation.

Putting Things Together

Obstructive Lung Disease

- Peak pressure 50 cm H_2O, IPP 35 cm H_2O; auto-PEEP 8 cm H_2O
- Total rate 16 breaths/min
- Spontaneous VT 300 mL
- I:E ratio = 1:1.5
- SpO_2 100%
- pH 7.20, $PaCO_2$ 60 torr (8 kPa), PaO_2 215 torr (28.7 kPa)
- BP 90/60 mm Hg, heart rate 130–140 beats/min

Analysis – Patient L.W.

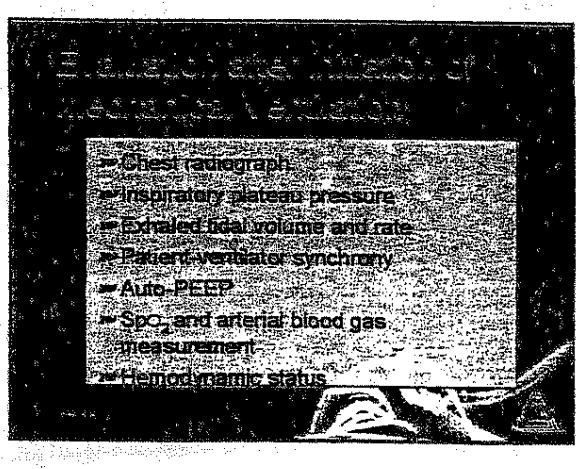
- Hypercapnia
- High peak airway pressure
- Wide peak-plateau pressure difference
- High auto-PEEP
- Low spontaneous VT despite pressure support
- Slightly high minute ventilation, increased $PaCO_2$
- Hypotension and tachycardia

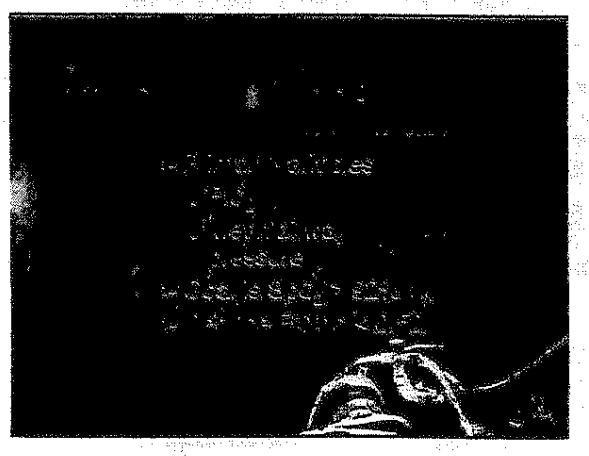
The Interactive Part

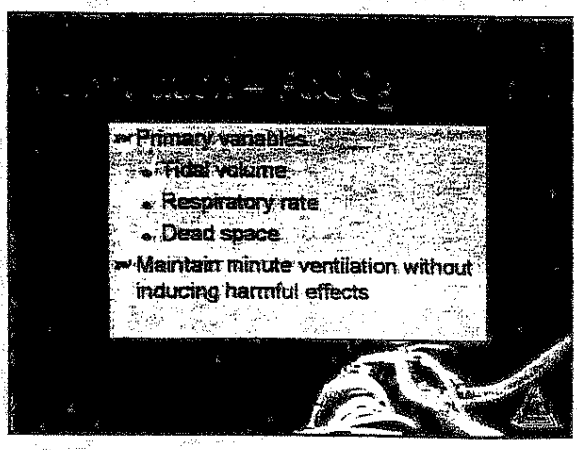
- What are the next steps?
- What variable(s) should be changed to improve the $PaCO_2$?
- What are the consequences of
  - –change in tidal volume ?
  - –change in respiratory rate ?
  - –change in ventilator mode?
  - –bronchodilators ?

Obstructive Airway Disease

- Obstructive diseases require adequate expiratory time
- Beware of auto-PEEP
- $PaCO_2$ should be kept at patient's baseline level







Lung injury in MV patients: WHY & HOW?

- Damage is induced by alveolar over distension & degree of injury depends on magnitude, frequency & duration of physical stretching.
- Regional variation in Lung Compliance may be present & result in variable small airway & alveolar stretching and over inflation.
- Repeated opening and closing (complete) of alveoli from positive pressure ventilators may predispose to barotrauma.

ARDS: Functional Lung Zones

- Heterogeneous Changes in Lung Parenchyma
- Varying degree of V/Q mismatch + shunt
- Low regional Lung compliance
- High regional Airway Resistance
- Disease lung portion + + Vs not recruitable (most)
- Disease lung + + Vs Recruitable (small)
- Normal lung portion: (small)

Improving outcome in ARDS: Issues For Clinicians:

- ? Right Tidal Volume
- ? Maximal Paw: Peak, mean and Plateau
- ? Right PEEP
- ? Pharmacological Rx
- Newer Technique of MV

MV in ARDS: Lung protective Strategy

Alveolar recruitment without over distension of alveoli

- Pressure Control Ventilation
- Permissive Hypercarbia
- Open Lung Technique
- Inverse Ratio Ventilation
- Prone Position
- Nitric Oxide Inhalation
- Non Invasive Positive Pressure Ventilation

- **Open Lung Technique**: Goal is to keep PEEP level just above the "inflection point" (level at which alveoli collapse) in a lung pressure volume curve.
- Tidal Volume < 6 ml/kg,
- Driving pressure < 20 cm above the PEEP
- Pressure limited mode, permissive hypercarbia

Ref: Amato in N Eng J Med 1998; 338:347-54 & Am J Respir Crit Care Med 1995;152:1835-46

- **Permissive Hypercarbia**: To limit TV and Paw while allowing $PaCO_2$ to rise, to avoid lung injury (mean 66: range 38-158)
- TV < 6 ml/kg
- Tracheal gas insufflation to flush out CO_2 from the dead space

Conclusion: It is safe and leads to better outcome

Ref: *Hickling in Intens Care Med 1990;16:372-77*
Gentilello in J Trauma 1995; 37:846-52
Kuo in Am J Respir CCM 1996;154:612-16

Inverse Ratio Ventilation

- Normal I:E ratio is 1:2 to 1:4
- IRV uses extended Inspiratory time to limit I:E ratio to <1:1 up to 2:1.
- Often used with PC
- Sustained high mean Paw leads to recruitment of collapsed alveoli, improved oxygenation
- decreased dead space ventilation and shunt
- Precaution: Auto PEEP occurs, sedation is essential, monitor cardiac function.
- Ref: *Marcy in Chest 1991;100:494-504*
  Shanholtz in Am J Respir CCM 1994;149:1354-58
  Abel in Thorax 1998;53:292-94

Pressure Control Ventilator: Goals:

- Peak airway pressure $\leq$50 cm H_2O, ? 40 cm
- Plateau pressure $\leq$30 cm H_2O (? 35 is safe)
- High Inspiratory Flow & Time
- Low TV (5-6ml) but nearly same MV, High RR
- Increased Mean Paw,
- SaO_2 > 92% (90), allow $PaCO_2$ to increase
- Near Normalization of arterial pH,
- Acceptable oxygen delivery

Liquid ventilation in ARDS

- Liquid Ventilation using Perflucarbon, total or partial, as an adjunct to conventional ventilation
- Biologically inert compound with low surface tension, high respiratory gas solubility.
- Distributed primarily to the dependent portion of the lung (atelectetic, collapsed lung)
- **Advantages**: Reduces alveolar surface tension, recruitment of additional lung tissue for ventilation, improve V/Q match, removal of cellular debris
- *Ref: Fuhrman Crit Care Med 1991; 19:712-722*
  Hirschl in JAMA 1996; 275:383-89 & Ann Surg 1998; 228:692-700

Clinical Trials	Stewart et al, 1998	Brochard et al, 1998	Brower et al, 1999	ARDS Net, 2000
N=Patient	120	116	52	861
TV				
Traditional	10.8	10.3	10.2	11.8
Lower	7.2	7.1	7.3	6.2
TV/K/PBW				
Traditional	12.2	11.3	10.2	11.8
Lower	8.1	7.8	7.3	6.2
Mortality				
Traditional	47	38	46	40
Lower	50	47	50	31

Main Outcome Variables

ARDS Network: NEJM vol. 342: 1301-08

Variables	Low TV Gr	Traditional. TV	P value
Death %	31	39.8	0.007*
Breathing s.	65.8	55	< 0.001*
# Ventilator Free days	12 $\pm$ 11	10 $\pm$ 11	0.007*
Barotrauma	10	11	0.43
# of days without MODS	15 $\pm$ 11	12 $\pm$ 11	0.006*

Reasons for better outcome

ARDS Network: NEJM vol. 342: 1301-08

- # Patients enrolled high which allowed the modest differences to manifest
- Exclusion of Pt. with severe co-morbidity
- Low Tidal volume in contrast to high TV*
- Relatively high PEEP with low TV
- Low Plateau pressure and ? High mean Paw
- ? Better oxygen delivery
- ? Correction of Respiratory acidosis with Bicarb

Prone Position in ARDS

- 55-60 % respond to prone positioning
- Repositioning is variable from 2 – 12 hr.
- Complication: Accidental extubation, loss of vascular access, nerve injury, facial edema, pressure sores on face, shoulder, knee, ankle, dislocation of intraocular lenses
- WVU experience: Use of Vollman Proner Device
- Support of cushions and foam pads
- Team Approach: need 4- 5 people to do it safely

Ref: Vollman in Dimens Crit Care Nurs 1997;16:184-193

Prone Position in ARDS

- Improve oxygenation without affecting CO2
- Improve ventilation of the dorsal areas as they become nondependent...alveolar recruitment
- Better perfusion in dorsal areas
- .....better V/Q match.
- Responders: Increase in PaO2 by > 10 or PaO2/FiO2 ratio by 30-60 , usually in 30 min, may be up to 2 hrs. Also do it early

Ref: Blanch in Intens Care Med 1997;23:1033-39
Jolliet in Crit Care Med 1998;26:1977-85

New Modality To Improve Oxygenation

- Nitric Oxide Inhalation,
- Extra corporeal CO_2 removal,
- Extra Corporeal Membrane Oxygenation
- Additive beneficial effect of prone position, nitric oxide and almitrine bismesylate on gas exchange and O_2 transport in ARDS
  - N = 12 patients 67% mortality

Ref: P Jolliet et al; CCM 1997 p786-

PEEP Level Selection and Adjustment

- "Best PEEP" = via static pressure-volume curve
- PEEP set above the lower inflection point :10-15 cm
- "Open lung approach" : Provide least necessary PEEP
- Keep alveoli open at the end of exhalation
- Measure lung compliance, Keep auto PEEP low to 0
- $FiO_2 < 0.5$ ($PaO_2/FiO_2 > 300$)
- Observe for potential complications

Avoid Oxygen Toxicity

- Keep $SaO_2 \geq 90\%$, (≤ 95 % is ok), $FiO_2 \leq 0.5$, $FiO_2 \geq 0.6$ can be toxic & ≤ 0.4 can be tolerated for a 1ong time.
- Permissive hypoxemia (SaO_2 85 to 88 %) in selected cases: Minimize the adverse effects by use of sedatives, etc. & keep adequate DO_2 (high Hb, CI), monitor SvO_2.
- Lung Protective Strategy

Patient Monitoring during MV

- Patient's **comfort level**, **breathing pattern**
- **Physiological**: RR, HR, BP, Urine output
- **Hemodynamic** (optional): PAOP, CO, DO_2, SVO_2
- **Gas Exchange**: SpO_2, End tidal CO_2, ABGs, & PaO_2 / FiO_2 ratio.
- **Airway Pressure & Graphics**: Peak, Mean & Plateau pressures, PEEP, and Auto PEEP, Pressure Volume & Flow Volume Graphics.
- Bicore monitoring in special cases

Issues In Mechanical Ventilation

- Increase in infection rate (ventilator associated pneumonia)
- Endotracheal tube related problems: (sinusitis, laryngeal injury, tracheal stenosis, tracheomalacia)
- Psychological issues
- Allow the lung and body to heal

Cardio-Vascular Impairment: Rx

- Adequate volume replacement and resuscitation
- Use of vasoactive drugs
- Hemodynamic monitoring may be necessary
- Experimental: Synchronize ventilator breath rate to cardiac contraction (airway pressure decreased during systole, low VT, high RR)

Cardio-Vascular Impairment

Multiple causes of adverse cardio-vascular effects:

- Decreased venous return & cardiac filling: Low CVP, PAOP, CI, BP, increased HR & (sometimes) Pulsus Paradoxus .... Good co-relation with high plateau and Mean airway pressure (but, ± with Peak pressure).
- Abnormal septal movement, RV dysfunction.

Patient -Ventilator Asynchrony/ Dysynchrony:

Can occur throughout the respiratory cycle:

1. Inappropriate Mode, Tidal Volume, Flow rate, I:E ratio, PEEP, and inadequate sensitivity to detect the patient's own effort.
2. Small size (diameter) ET tube: High W.O.B.
3. Significant hypoxemia, acid base abnormalities
4. 4. Inadequate sedatives or analgesics: Discomfort

Ventilator Dysynchrony Rx:

- Appropriate use of sedatives & analgesics & judicious, limited use of paralytic drugs
- Adjust ventilator according to the underlying pathology
- Dynamic Process: Individual need & response is variable: The ventilator setting may need frequent changes - "a cookbook approach may not work".
- Use of pressure support.

Improving patient tolerance of the respirator

- Supportive care for neurobehavioral abnormalities
- IV Sedation: Benzodiazepines, opioids, benadryl, etc.
- Positive reinforcement
- Develop practice guidelines for sedation and muscle paralysis

Fontaine, et al. Critical Care Clinics Oct., 1994

Respiratory distress in ventilated patients

- Respirator related problems
- Progression of the underlying disease
- Development of a new medical problem
- Intervention and procedures in the ICU
- Miscellaneous: hyperthermia, DT's, seizures, IV lipids, drugs (bronchodilators, vasodilators)

Respirator related problems

- Improper ventilator settings: i.e. abnormal TV, flow rate, I:E ratio, auto PEEP, inadequate sensitivity, FiO_2, or mode of ventilation
- Ventilator and breathing circuit problem
- Artificial airway problems: malposition, cuff failure, blockage by thick secretions, TE fistula

Medical problems

- Agitation, restlessness, pain
- Aspiration, atelectasis, nosocomial pneumonia, bronchospasm, Barotrauma (pneumothorax, BPD)
- Impaired hemodynamics, fluid overload, pulmonary edema, ARDS, Pulmonary embolism
- Abdominal catastrophe
- Sepsis

Ref: Glauser in Am Rev Respir Dis 1988;138:458-65, Fontaine, et al. Critical Care Clinics Oct., 1994

Causes of distress in ventilated patients

- Anxiety, fear, pain
- Sleeplessness
- Inability to speak
- Immobility, noise
- Confusion, thirst
- Disorientation of time, day, date
- Procedures

Fontaine, et al. Critical Care Clinics Oct., 1994

Causes of distress in ventilated patients

Fontaine, et al. Critical Care Clinics Oct., 1994

- Constant bright light and commotion in the ICU
- Unfamiliar people & machinery
- Helplessness
- Sore body, mouth, throat, nose
- Being tied down
- Unable to communicate
- Tugging of ventilator tubing

Initial assessment and management

- Check Ventilatory settings & circuit leaks for connections, correlate exhaled TV to inhaled TV
- Scan bedside monitor for changes in HR, BP, SaO2, PA pressure
- Examine patient for air entry, diminished chest wall movement, secretions (ET suctioning if necessary)
- Start 100% oxygen with manual ventilation

Initial assessment and management (II)

- Review hemodynamics
- Exclude malposition or occluded airway
- Chest x-ray (R/O Pneumothorax), cross table lateral
- Assess if asynchrony present; change mode of ventilation to AC, increase rate
- Measure auto PEEP; if >5, make necessary changes
- Consider sedation

Weaning: What will be covered

- General Principles
- Weaning Parameters : Conventional and Newer
- Termination of weaning
- Role of Weaning Protocols
- Failure to Wean: causes and management
- Role of Tracheostomy
- Long term Care Hospitals for chronic ventilated patients

Weaning: Discontinuation of ventilator

- Process of withdrawing a mechanical ventilator from a patient
- Weaning from Ventilator is very common in ICU.
- Is there a problem?
- Two large trials have shown 25 % failure rate on first attempt (Brochard et al in Am J Resp CCM 1994, Esteban in NEJM 1995).
- Difficult to wean patient can cause significant clinical, economical and ethical problems.
- A team approach or protocol driven weaning leads to rapid weaning and better outcome
- Guidelines published in CHEST supplement, Dec 2001.

Weaning: Discontinuation of ventilator

- Basic Evaluation:
- Resolution of original clinical problem
- Patient should have adequate pain relief, less sedated and made comfortable.
- Acceptable acid base status
- Stable hemodynamics on clinical evaluation (HR, BP, RR, Temperature, cardiac output)
- Determining the optimal time to discontinue ventilator can be difficult
- An experienced physician can have an intuition as to the likely outcome of a weaning trial.
- develop a "6th sense"

Weaning: Methods of Assessment

- Weaning parameters: must be accurate, reliable, reproducible, safe, inexpensive
- Understand physiological meaning
- Standardized
- Nothing is absolute -
- Know your patient

Weaning Criteria: Baseline

- Gas Exchange : (ABG) $PaO_2 > 70$ on $FiO_2 < 0.5$, $PaCO_2$ 35-45, normal pH
- PEEP < 6 cm, $PaO_2 / FiO_2 \geq 300$,
- Intra Pulmonary Shunt (QS/QT) $\leq 20\%$,
- Mode of ventilation: AC, SIMV, CPAP, PS, T piece
- Level of consciousness
- Ability to protect airway (for extubation)

Weaning Techniques

- Majority of the patients with normal CNS drive, good cardio–pulmonary and muscle function will wean with any technique !!!
- **A trial of spontaneous breathing via a T piece (1-2 hr) or CPAP with PS (7-8cm)**
- Pressure support 7 cm or more (able to overcome the inspiratory W.O.B.)
- **Use of Synchronize IMV**
- Mandatory Minute Ventilation (MMV)
- Intermittent Demand Ventilation (IDV).

Weaning Techniques.....II

- Volume support
- Automatic tube compensation
- Adaptive support ventilation
- *"Intuition of an experienced Intensivist*
- *Cold turkey" - sink or swim, "Flip a coin"*
- *Extubation followed by early CPAP or BiPAP by nasal or full face mask*

Weaning Parametrs: Basic...

- **Pulmonary mechanics**: ***RR*** $\geq$ 10 & $\leq$ 30, ***TV Sp*** $\geq$ 5 ml/kg, ***TV sp*** > 350- 400 ml is a good indices for success. If TV < 200 ml – failure, *MV* $\geq$5 and $\leq$ 10 L, ***Lung compliance*** Cdyn (= TV/ PAP – PEEP) > 30 ml/cm,
- **Muscle Strength: *NIF*** > -30 cm (N = -60 to 100). ***FVC*** $\geq$ 15 ml/kg or >1 L, (N = 65 - 75 ml/kg)
- Sensitivity and specificity of individual parameter is very low. 4/6 criteria must be present for successful outcome.
- **Rapid Shallow Breathing Index** = f/TV (L) $\leq$ 90 , no extubation if > 105. Marginal between 90 –105. Single most sensitive and reliable indicator

Weaning.... II

- Clinical Observation: Paradoxical motion of abdomen, Respiratory alternans. Abnormal motion 2° to increased load, suggests respiratory muscle fatigue
- RSBA: Breaths per min / TV(L) = Rapid, Shallow Breathing Index (breathing pattern)
- F/TV = 60-90 (> 105, failure +++)
- If T_I / T_{TOT} is 0.3 to 0.4, then increased fatigue is likely

Termination of Weaning Trial

- HR > 110-120/min (>25% baseline), f > 30 -35/min
- BP rise > 25%, diastolic >100 or drop in SBP, Cardiac arrhythmias, ST-T wave changes, or chest pain
- Significant hypoxemia or high $PaCO_2$
- Paradoxical motion of abdomen, Respiratory alternant. Abnormal motion 2° to increased load, suggests respiratory muscle fatigue
- Asynchronous breathing, Diaphoresis & nasal flaring increased patient effort, Increased sternomastoid activity, retraction seen in the suprasternal, supraclavicular &/or intercostal spaces
- Altered level of consciousness, agitation
- Development of cyanosis is a late sign.

Patient Monitoring during MV

- Patient's **comfort level, breathing pattern**
- **Physiological**: RR, HR, BP, Urine output
- **Hemodynamic** (optional): PAOP, CO, DO_2, SVO_2
- **Gas Exchange**: SpO_2, End tidal CO_2, ABGs, & PaO_2 / FiO_2 ratio.
- **Airway Pressure & Graphics**: Peak, Mean & Plateau pressures, PEEP, and Auto PEEP, Pressure Volume & Flow Volume Graphics.
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Improving patient tolerance of the respirator

Fontaine, et al. Critical Care Clinics Oct., 1994

- Supportive care for neurobehavioral abnormalities
- IV Sedation: benzodiazepines, opioids, benadryl, etc.
- Positive reinforcement
- Develop practice guidelines for sedation and muscle paralysis

Failure to Wean: Causes

Up to 25% received prolonged ventilation

- Persistent pathology: i.e. sepsis, ARDS, COPD, underlying lung disease
- High ventilation requirement: high MV, V/Q mismatch, increased VD/VT or RQ , increased work of breathing
- Cardio - vascular limitation (decrease CO)
- Diminished muscle strength
- Inadequate pain relief
- Psychological, respirator dependency
- Miscellaneous: Abnormal central drive, CNS injury, flail chest

FAILURE TO WEAN: CAUSES... II

- Excessive airway secretions
- Drugs: Sedatives, narcotics, paralytic agents, steroid therapy
- Malnutrition, hypothyroidism
- Electrolyte imbalance; low K, PO_4, Mg, Ca
- Lack of muscle strength, disuse atrophy, discoordination of respiratory muscles
- Neuropathy, Myopathy of critical illness, Cervical spine or Phrenic nerve injury

Respirator related problems

- Improper ventilator settings: i.e. abnormal TV, flow rate, I:E ratio, auto PEEP, inadequate sensitivity, FiO_2, or mode of ventilation
- Ventilator and breathing circuit problem
- Artificial airway problems: malposition, cuff failure, blockage by thick secretions, TE fistula

Medical problems

- Agitation anxiety, restlessness, pain, fear, Sleeplessness
- Aspiration, atelectasis, nosocomial pneumonia, bronchospasm, Barotrauma (pneumothorax, BPD), Procedures
- Inability to speak, Immobility, noise, thirst
- Confusion, Disorientation of time, day, date
- Impaired hemodynamics, fluid overload, pulmonary edema, ARDS, Pulmonary embolism
- Abdominal catastrophe, Sepsis

Ref: **Fontaine, et al. Critical Care Clinics Oct., 1994,** *Glauser in Am Rev Respir Dis 1988;138:458-65, Fontaine, et al. Critical Care Clinics Oct., 1994*

Work Of Breathing By Respiratory Muscles

- Physiologic work + Imposed work
  - (Elastic work to expand lung and chest wall, flow resistive work to overcome airway resistance)

PLUS

Resistive work imposed by breathing apparatus

- Range 0.3 to 0.6 Joule/L

Bicore Monitor CP-100

- Bicore smart cath esophageal 7F (35-40 cm mark) balloon, NG tube 16 FR
- Measurement of PAW, Peso, Air Flow

  From this, another 25 variable are monitored/calculate
- Flow transducer
- Automated inflation volume of 0.8 ml, frequency response of 30 Hg.

Increase Work Of Breathing

- Decrease lung and/or chest wall compliance
- Bronchospasm
- Increase MV and VD/VT
- Increase auto PEEP
- Smaller ET tube diameter
- Altered sensitivity: Triggering the ventilator

Bicore Monitor

Strength		Endurance	
WOB	0. 3 - .6 J/L	P_O 1 H_2O	*2-4 cm*
P Max	> 30 cm	*PTI*	*0.05 - 0.12*
Pes	5-10 cm	*Ti/Ttot*	*0.3 - 0.4*
MV	5-10 LPM	*F/TV (L)*	

Weaning Techniques: Nonconventional

- Special measurements: Research
- VO2 Resp < 5%
- TTdi (time tension index = endurance <0.15)
- EMGdi hi/lo > 80%, Ti / TTOT, Power spectrum shift in EMG
- Pdi / Pdi max < 0.40 , WOB 0.3-0.6 J/L,
- VD/VT < 0.6, VO2, Change in Pes 5-10 cm (BiCORE)
- PTI (pressure time index 0.05-0.12)
- P0.1 (respir. drive) 2-4 cm , > 6 cm = failure, < 2 = good

Airway pressure generalized at 0.15 sec. after initiating inspiration against close airway

Managing patient with weaning Difficulties

- Identify the cause, correct the underlying problem
- Team Approach (physician, nurse, RT, PT, Dietitian, family members)
- Adequate rest, sleep, analgesics, sedatives and antidepressant
- Psychological support, positive reinforcement, OOB
- Optimal bronchodialtors, good pulmonary toilet, tracheostomy
- Proper ventilator settings.
- Respiratory muscle strengthening exercises
- Tertiary care or Rehab hospital

Non Invasive Positive Pressure Ventilation

- Assisted Mechanical Ventilation without an artificial airway is designed to inflate the chest with positive pressure applied through a mask
- Mask: nasal or full face
- CPAP, BiPAP : Bilevel Positive Airway Pressure
- **ADVANTAGES :**
  Patient comfort & independence
  Decreased need for sedation & muscle relaxants
  Low incidence of V-A-P, sinusitis

NIPPV: Suitable Candidates

CLINICAL ASSESSMENT:

- Moderate to severe respiratory distress: RR >25, using accessory muscles, paradoxical breathing.
- Acute or chronic hypercarbia: $PaCO_2$ >45, pH <7.35, but > 7.1
- Acute pulmonary edema
- Hypoxemic respiratory failure: Acute Lung Injury (PaO_2/FiO_2 < 300)
- Post extubation: Ventilatory support

NIPPV: Suitable Candidates (II)

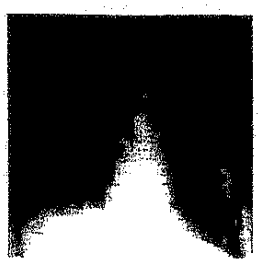
- **DIAGNOSIS:**
  * Exacerbation of acute COPD
  * Acute respiratory failure due to pneumonia, acute asthma, post operative resp. failure, and neuromuscular weakness
- Patient must be awake & co-operative, able to protect the airway (no or low risk for aspiration), & understand & participate.

Permissive Hypercapnia

- Acceptance of an elevated $PaCO_2$, e.g., lower tidal volume to reduce peak airway pressure
- Contraindicated with increased intracranial pressure
- Consider in severe asthma and ARDS
- Critical care consultation advised

Putting Things Together

Acute Lung Inflammation / ARDS



J.T. is a 68-kg, 42-yr old female admitted after a drug overdose complicated by emesis and aspiration. Intubation and mechanical ventilation are initiated in the emergency department.

Putting Things Together

Acute Lung Inflammation / ARDS

- Peak airway pressure 52 cm H_2O
- Inspiratory plateau pressure (IPP) 48 cm H_2O
- Auto-PEEP 0 cm H_2O
- SpO_2 88%
- pH 7.38, $PaCO_2$ 36 torr (4.8 kPa), PaO_2 57 torr (7.6 kPa)

Analysis – Patient J.T.

- Hypoxemia with FIO_2 at 1.0
- High inspiratory plateau pressure
- Adequate ventilation
- Sedation/neuromuscular blockade

The Interactive Part

- What are the next steps?
- What variable should be changed to improve PaO_2?
- What are the consequences of the following ventilator changes?
  - Increased PEEP
  - Decreased tidal volume
  - Increased respiratory rate

Acute Lung Injury

- Decreased lung compliance results in high airway pressures
- Low tidal volume often needed
- Maintain IPP $\leq$ 30 cm H_2O
- PEEP to improve oxygenation

State of the Art

Worsening Oxygenation in the Mechanically Ventilated Patient

Causes, Mechanisms, and Early Detection[1,2]

FREDERICK L. GLAUSER, R. CRYSTAL POLATTY, and CURTIS N. SESSLER

Introduction

Mechanical ventilation is commonly employed in the intensive care unit (ICU) (1–5). In our 12-bed Medical-Respiratory ICU at the Medical College of Virginia, an average of 7 ± 1.8 patients are receiving mechanical ventilation at any one time (12-month survey). Although this modality is often life-saving (or at least life-prolonging), patients may experience significant reductions in oxygenation. It is our clinical impression that hypoxemia, or impaired oxygenation (these terms will be used interchangeably), in critically ill, mechanically ventilated patients is a common event that has not been specifically addressed in the medical literature (6, 7). In this article, we will first briefly review the physiology and determination of impaired oxygenation. We will then review the conditions that result in worsening oxygenation in depth and present guidelines for rapidly identifying the causes of impaired oxygenation.

Physiology of Impaired Oxygenation

Tissue oxygenation, which is dependent upon adequate oxygen delivery and extraction, and not the Pa_{O_2} per se, is the critical factor for organ survival and function (8). The arterial oxygen content (Ca_{O_2}) depends upon the amount of hemoglobin present, the position of the oxyhemoglobin dissociation curve, the Pa_{O_2}, and the affinity of oxygen for hemoglobin. The Ca_{O_2} may be normal, and inadequate tissue oxygenation may be present if the cardiac output is insufficient to meet demands. Finally, tissue oxygen extraction depends upon oxygen delivery, the ability of hemoglobin to offload oxygen, and the affinity of cellular mitochondria for oxygen (8).

Physiologic mechanisms that result in inadequate pulmonary oxygen uptake include ventilation-perfusion (V/Q) mismatching, shunting, hypoventilation, low $P_{A_{O_2}}$ (from an increase in altitude or a decrease in $F_{I_{O_2}}$), and diffusion abnormalities. A low Pa_{O_2} and widened alveolar-arterial oxygen ($A\text{-}a_{O_2}$) difference (see below) are associated with V/Q mismatching and shunting. An elevated $P_{A_{CO_2}}$ indicates some degree of alveolar hypoventilation that may be "absolute," i.e., the result of a decrease in minute ventilation (V_E) or "relative," i.e., due to an increase in dead space (V_D/V_T) with an unchanged or increased V_E. In these situations, the $A\text{-}a_{O_2}$ difference is not increased. However, if V/Q mismatching or shunting is also present, the $A\text{-}a_{O_2}$ difference will widen. Low $F_{I_{O_2}}$ and diffusion abnormalities are rarely clinically significant problems.

Impaired oxgyenation is not always due to worsening lung problems. For example, under certain circumstances a reduced cardiac output with a low $P_{V_{O_2}}$ causes a fall in arterial oxygenation, particularly when regional gas exchange abnormalities exist. A fall in $P_{V_{O_2}}$ from approximately 40 to 30 mm Hg in patients with stable V/Q mismatching or a 30% constant shunt (and constant minute ventilation) decreases the Pa_{O_2} from approximately 55 to 45 mm Hg (9, 10). Conversely, when oxygen consumption falls, Pa_{O_2} may improve even if cardiac output remains stable or decreases.

Determination of Impaired Oxygenation

It is important to consider the Pa_{O_2} in relation to the $P_{A_{O_2}}$ or $F_{I_{O_2}}$ when confirming that impaired oxygenation is present. This can be done by calculating the $A\text{-}a_{O_2}$ difference, the a/A_{O_2} or the $a/F_{I_{O_2}}$ ratio (table 1) (11). Because the $A\text{-}a_{O_2}$ difference increases as the $F_{I_{O_2}}$ is raised, the aforementioned ratios are particularly helpful when supplemental oxygen is administered. In essence, these are "extraction" ratios that reflect the ability of the pulmonary capillary blood to remove or "extract" oxygen from the alveolus. If the patient's pulmonary condition and cardiac output are stable, these ratios will not change significantly as the $F_{I_{O_2}}$ varies. The alveolar P_{CO_2} is taken into account when calculating the a/A_{O_2} ratio. However, for most clinical situations where the Pa_{CO_2} is not fluctuating widely, the $a/F_{I_{O_2}}$ can be used because it is simpler to calculate.

Causes, Mechanisms, and Detection of Impaired Oxygenation

We will arbitrarily divide our discussion into (*1*) ventilator-related problems, (*2*) progression of the underlying disease process, (*3*) the onset of a new problem, or (*4*) certain interventions, procedures, and medications, all of which can result in impaired oxygenation (table 2).

Ventilator-related problems include endotracheal (ET) and tracheostomy tube malfunctions, improper ventilator settings, and ventilator and breathing circuit malfunctions (12). Proximal or distal migration of the ET tube or transient changes in the tube cuff (or tip) relative to the vocal cords due to flexion, extension, or rotation of the patient's neck are common events (7, 13, 14). In individual cases, ET tube displacement may be greater than 5 cm, although the average is about 2 cm (13). A low-positioned ET

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[1] From the Department of Medicine, Pulmonary Division, Medical College of Virginia/McGuire Veterans Administration Hospital, Richmond, Virginia.

[2] Requests for reprints should be addressed to Frederick L. Glauser, M.D., Chief, Pulmonary Division, Medical College of Virginia, 1200 E. Broad St., Box 50, Richmond, VA 23298-0001.

TABLE 1

DEFINITIONS OF IMPAIRED OXYGENATION*

	Normal Values	Abnormal Values
Pa_{O_2}	65–70 mm Hg	< 65 mm Hg
$A-a_{O_2}$	15–20 mm Hg	> 20 mm Hg
a/A_{O_2}	0.8–0.85	< 0.7
a/F_{IO_2}	> 400	< 350

* Values are somewhat arbitrary; a fall in any value greater than 10 to 15% from the patient's baseline can also be considered clinically significant.

TABLE 2

CAUSES OF IMPAIRED OXYGENATION IN CRITICALLY ILL, MECHANICALLY VENTILATED PATIENTS

1. Ventilator-related problems
   a. Endotracheal/tracheostomy tube malfunctions
   b. Improper ventilator settings
   c. Ventilator and breathing circuit malfunctions
2. Progression of underlying disease process
   a. Adult respiratory distress syndrome
   b. Cardiogenic pulmonary edema
   c. Pneumonia
   d. Airway obstruction—asthma and COPD
3. Onset of a new problem
   a. Simple, tension, anterior loculated pneumothoraces
   b. Lobar atelectasis
   c. Gastric aspiration
   d. Nosocomial pneumonia
   e. Pulmonary emboli
   f. Fluid overload
   g. Microatelectasis
   h. Bronchospasm
   i. Retained secretions
   j. Shock
4. Interventions and procedures
   a. Endotracheal suctioning
   b. Position changes
   c. Chest physical therapy
   d. Bronchoscopy
   e. Thoracentesis
   f. Peritoneal dialysis
   g. Hemodialysis
5. Medications
   a. Bronchodilators
   b. Vasodilators
6. Miscellaneous

tube results in ventilation of one lung, with an increased risk of barotrauma and decreased venous return (7, 13–15). Approximately 10% of ICU patients experience right main stem bronchus intubation (7, 13–15). This can be detected by noting the presence of unilateral breathsounds over the ipsilateral main stem bronchus. Caudal migration of the ET tube relative to the nares or mouth (compared to the previous position) supports this diagnosis, and withdrawal of the ET tube with subsequent return of bilateral breathsounds confirms and corrects this condition.

An ET tube positioned too high may lead to tracheal extubation with subsequent alveolar hypoventilation, a problem that is less common in patients with tracheostomy tubes. If the ET tube is above the vocal cords, the patient cannot be adequately ventilated, can phonate, and air escapes through the nose and mouth. Cranial migration of the ET tube is also present. Cuff leaks, which accounted for 34% of ET tube complications in one study (15), result in alveolar hypoventilation and loss of PEEP. In this situation, cuff pressure cannot be maintained. For a variety of reasons, the ET tube cuff may fail to "seal" the airway (15).

Rarely, ET tube kinking (typically with nasotracheal intubation using soft rubber tubes), which is often positional, or plugging of the tube with inspissated secretions or blood will not allow ventilation or suctioning (14). Replacement of the ET tube corrects this problem.

Occasionally, the esophagus is intubated when ET tubes are repositioned. Absent chest excursion and "breathsounds" heard loudest in the abdominal region suggest this diagnosis (which may be difficult to detect or confirm). If immediately available, endotracheal intubation can be confirmed with fiberoptic bronchoscopy and/or by measuring exhaled CO_2 (16).

Inadvertant or inappropriate changes in any of the ventilator settings including F_{IO_2}, tidal volume (V_T), respiratory rate (f), PEEP, inspiratory flow rates, and inspiratory/expiratory (I/E) ratios can potentially result in hypoxemia. In one series, human error was responsible for 38.6% of all ventilators incidents (17). Ventilator settings may be appropriate, but an electrical and/or mechanical malfunction results in fluctuations in F_{IO_2}. The oxygen percent selector setting should reflect the desired F_{IO_2}. Gas mixing accuracy is generally within 3% with modern ventilators; however, this should be confirmed by checking the visual display of the measured oxygen concentration. If a discrepancy exists, the F_{IO_2} should be confirmed with another oximeter. Because many ventilators do not establish the intended change in F_{IO_2} for 10 to 20 s after the dial has been changed, several minutes should elapse before rechecking the F_{IO_2}.

Mechanical failure (inability of the ventilator to cycle or loss of pressure and/or effective V_T) accounted for 14% of all ventilator problems in one series (18). Expired minute volume should be measured and compared to calculated ventilator delivered (IMV + spontaneous) volume. Many ventilators display measured expired minute volume; however, if questions remain, volume should be measured directly using an appropriate measuring device.

Malfitting or uncoupled breathing circuit connections, defective material, or mechanical obstruction from kinks or intraluminal fluid may cause inadequate gas delivery. When a leak is suspected, the entire circuit must be closely evaluated. With a leak in the gas delivery circuit (anywhere between the ventilator and the ET tube), peak airway pressure is often less than previously measured.

Inadvertent or unwise changes (either decreases or increases) in PEEP may, rarely, worsen V/Q relationships, leading to impaired oxygenation (19, 20). PEEP is typically used in patients with the adult respiratory distress syndrome (ARDS), a diffuse, bilateral interstitial and alveolar process that does not involve all lung areas equally (21). Excessive PEEP levels may overdistend the more compliant, normal alveoli (19–21). When alveolar pressure exceeds capillary pressure, blood flow decreases or ceases to the affected units. V_D/V_T increases in these units with a resultant increase in P_{ACO_2} (unless V_E increases). Blood flow is diverted to poorly ventilated or unventilated units, leading to V/Q mismatch and shunting result-

ing in hypoxemia. These deleterious effects of PEEP may be seen as the ARDS is resolving, because pulmonary edema is cleared in a nonuniform fashion. The presence of excessive PEEP may be detected by decreasing the PEEP by 3 cm H_2O for 3 min, obtaining an arterial blood gas, and returning the PEEP to the original level. If the Pa_{O_2} falls by 20% or greater compared to baseline levels, excessive PEEP is not present. Conversely, no change or a rise in Pa_{O_2} implies the PEEP level was too high.

Hypoxemia can also be the result of a fall or complete loss of PEEP. The level of PEEP can be determined by observing that airway pressure (via the ventilator gauge) is positive at end-exhalation.

Patients with predominantly unilateral pulmonary infiltrates may experience substantial falls in Pa_{O_2} at higher PEEP levels (19). The clinician may incorrectly interpret the fall in Pa_{O_2} as a worsening of the patient's ARDS and increase the PEEP level, thus initiating a vicious cycle of worsening oxygenation, further increases in PEEP, worsening oxygenation, etc.

Finally, in the past, in order to obtain a "true" reading, the pulmonary wedge pressure was measured after removing the patient from mechanical ventilation and PEEP (22). This practice resulted in significant hypoxemia in these critically ill patients. Most centers have banned this practice, and the pulmonary wedge pressure is obtained without lowering the PEEP level.

Patient-related problems include rapid progression of the *underlying disease process* or the onset of a *superimposed disorder* (a new disease process or pathologic event) (table 2). An in-depth discussion of the causes and mechanisms for the impaired oxygenation in these disorders is beyond the scope of this review, and the interested reader is referred to standard textbooks. However, pneumothorax and atelectasis will be discussed in some detail because they are relatively frequent events in critically ill, mechanically ventilated patients.

Pneumothoraces can be arbitrarily classified as simple (no tension), tension, and loculated. The new onset of unilateral, decreased breath sounds and respiratory distress suggests the presence of a tension pneumothorax (or extensive atelectasis, see below) (23–30). Findings consistent with the presence of a tension pneumothorax include diminished breath sound, hyperresonance, bulging intercostal spaces, contralateral tracheal shift, internal jugular venous distention, subcutaneous emphysema, tachycardia, and systemic hypotension. Pulmonary interstitial emphysema on a previous chest roentgenogram is a valuable clue to impending pneumothorax (23, 24). In one series, 17 of 82 mechanically ventilated patients with respiratory failure developed radiologic evidence of pulmonary interstitial emphysema. Eight of these patients subsequently developed a tension pneumothorax (25). The initial therapeutic approach is to insert through the chest wall a small-gauge needle that is attached to a liquid-filled syringe. If a tension pneumothorax is present, air will bubble under pressure through the liquid. Definitive therapy consists of thoracostomy tube insertion.

Fig. 1. Patient with anterior pneumothorax and bilateral pneumonias. Left heart border (*open arrows*) is more clearly seen compared to right heart border; left diaphragm (d) is depressed; left cardiophrenic angle is clearly seen (*solid arrow*); and cardiophrenic angles are asymmetric.

In our experience, anterior loculated pneumothorax is common and often difficult to diagnose in these patients (figure 1, table 3). An upright or bilateral decubitus chest film may allow free air to move to the superior aspect of the thoracic cage, making the pneumothorax more apparent. Treatment consists of chest tube placement.

Mucus plugging and resultant lobar or whole lung atelectasis may cause profound hypoxemia due to shunting and is characterized (on physical examination) by tubular breath sounds (increased sound transmission) and a dull percussion note. Atelectasis is confirmed by chest roentgenogram and may respond to vigorous chest physical therapy (CPT) and/or fiberoptic bronchoscopy. Marini

TABLE 3

RADIOLOGIC SIGNS OF AN ANTERIOR PNEUMOTHORAX IN THE SUPINE PATIENT

1. Asymmetric cardiophrenic angles
2. Lucent cardiophrenic angle
3. Unusual clarity or sharpness of heart or diaphragm
4. Basilar hyperlucency
5. Depressed diaphragm
6. Double diaphragm sign
7. Pericardial fat pad prominent
8. Visibility of inferior lung edge or other visceral pleural edge

and associates (31) compared the usefulness of these techniques in the treatment of acute lobar atelectasis in 31 ICU patients. They found that the addition of fiberoptic bronchoscopy with lavage to a vigorous respiratory therapy regimen was not helpful in patients who could undergo CPT treatments. However, they noted in 5 of 13 patients (48%) an increase in A-a_{O_2} difference of 25% (the actual Pa_{O_2} are not given) in those undergoing fiberoptic bronchoscopy. In contrast, the largest increase in this gradient after CPT was 14%. They conclude and we concur that "fiberoptic bronchoscopy is not required for reversal of acute lobar collapse in most cases and that it may be associated with adverse effects." We reserve fiberoptic bronchoscopy with lavage for patients (*1*) with refractory, life-threatening hypoxemia unresponsive to supplement oxygen, (*2*) who cannot tolerate positional changes or CPT, and (*3*) who do not respond to 24 to 48 h of CPT.

A variety of pulmonary and nonpulmonary *interventions and procedures* are performed on mechanically ventilated ICU patients. Some are "routine" (endotracheal suctioning, position changes, chest physical therapy), whereas others are specific diagnostic or therapeutic procedures (bronchoscopy, thoracentesis, peritoneal dialysis, hemodialysis). Although these procedures achieve their desired goals, all may be associated with worsening of oxygenation.

Tracheal suctioning, although effective in removing airway secretions, is associated with a variety of complications, including tracheobronchial mucosal trauma, microatelectasis, dysrrhythmias, cardiovascular collapse, sudden death, and hypoxemia (32–38). Mean Pa_{O_2} decreases vary from 10 to 39 mm Hg, but individual declines may be much greater (32–35). Hypoxemia can last as long as 15 min after suctioning (32). Most investigators feel suction-induced hypoventilation is the principle mechanism responsible for the fall in Pa_{O_2} (table 4). Others feel that reflex bronchoconstriction caused by mechanical tracheal stimulation is partly responsible for these findings (32).

Positional changes (39–44), particularly in patients with predominantly unilateral lung disease, are associated with falls in Pa_{O_2} when, through gravitational effects, blood is shunted through the dependent abnormal or "sick" lung. In one series, Pa_{O_2} fell approximately 30% from baseline in mechanically ventilated patients (35). Changes in position may also impair oxygenation in patients with ARDS, a bilateral disease (41).

Chest physical therapy includes postural drainage, manual percussion, chest vibration, and coughing maneuvers. CPT facilitates mucociliary clearance, increases expectorated sputum volume, and improves airway function in the mechanically ventilated patient (45–52). It is more effective in patients with copious, compared to those with scant, secretions and/or pneumonia (45, 48). Pa_{O_2} may fall (a mean decline of 20%) after CPT in patients who produce no or thin mucoid sputum (41, 44). Post-CPT hypoxemia may be due to bronchospasm or the migration of distal secretions to larger, more proximal airways, increasing V/Q mismatching. It is probably not due to the positional changes associated with CPT, at least in patients with COPD (52).

Fiberoptic bronchoscopy is associated with hypoxemia in spontaneously breathing, nonmechanically ventilated patients (53–59). Postbronchoscopy hypoxemia may persist for as long as 3 h in a small percentage of patients (54). Increasing intrapulmonic shunt, V/Q mismatching, bronchospasm, and occlusion of a main stem or smaller bronchus may be responsible for this fall in Pa_{O_2}. Surprisingly, postbronchoscopy hypoxemia (at least in one study) was less commonly encountered in mechanically ventilated compared to spontaneously breathing, nonintubated patients (57). This finding may be due to the fact that bronchoscopy is more often a therapeutic procedure in mechanically ventilated patients, i.e., for removal of secretions, reversal of lobar or whole lung atelectasis, and "improved gas exchange" (55). Lindholm and colleagues (55) noted minimal increases in Pa_{O_2} during and 15 min after bronchoscopy in 15 mechanically ventilated patients. However, they warn (without any objective evidence) that the risk of developing hypoxemia exists.

Thoracentesis has been associated with hypoxemia in some (60, 61), but not all, studies (62). Brandsetter and Cohen (60) found a small fall in Pa_{O_2} 20 min after thoracentesis, which persisted (to a lesser degree) for at least 2 h. These investigators also noted a direct relationship between the volume of fluid removed and the degree of hypoxemia present at 20 min after thoracentesis. Hypoxemia may, in some patients, be due to the development of unilateral (re-expansion) pulmonary edema (61). In others, it may be due to worsening V/Q relationships as pulmonary blood flow, which had been absent or low, increases to areas with persistant airway closure or alveolar collapse.

A fall in Pa_{O_2} is a consistent finding in spontaneously breathing, nonintubated patients undergoing upper gastrointestinal endoscopy (we are unaware of any studies performed in intubated, mechanically ventilated patients) (63–69). Pa_{O_2} falls as the endoscope is inserted and remains depressed during and for a short

TABLE 4

PROPOSED MECHANISMS FOR POST-SUCTIONING HYPOXEMIA

Depends on the following:
1. The amount of suction pressure and flow applied
2. The duration of suctioning
3. The catheter's internal diameter and sidebore orifice size
4. Hyperventilation prior to suctioning
5. The administration of supplemental oxygen
6. The amount of suction related small airway closure (atelectasis)
7. The initial Pa_{O_2}
8. The presence of intrapulmonic shunts
9. Suction-induced hypoventilation
10. Reflex bronchoconstriction

time after the procedure. Mean falls in Pa_{O_2} average 15 to 25%. Patients with chronic obstructive pulmonary disease (COPD) are more prone to endoscopically induced hypoxemia (69). The etiology of this endoscopically induced hypoxemia is unclear but is not related to the sedative administration, gastric aspiration, a history of cigarette smoking, or hypoventilation. Postulated mechanisms include: (*1*) insertion of the endoscope induces vagally mediated bronchospasm, (*2*) endoscopy releases prostaglandin F, which induces bronchospasm and/or vasospasm leading to V/Q mismatching and hypoxemia (66), and (*3*) narcotic (meperidine) premedication, particularly in the elderly patient, may lead to respiratory depression (65).

Peritoneal dialysis is associated with a multitude of pulmonary problems, including pleural effusions, gastric aspiration, basilar atelectasis, changes in pulmonary artery pressures, and hypoxemia (70–74). The intraperitoneal fluid may elevate the diaphragms, inducing basilar atelectasis, V/Q mismatch, and hypoxemia. Other investigators have not found any changes in oxygenation during dialysis (70).

Worsening arterial oxygenation is a common finding in patients undergoing hemodialysis (75–81). The fall in Pa_{O_2} is present within 10 min of initiating dialysis and persists, to a lesser extent, for the duration of the procedure (76, 77, 79, 80). The etiology of this worsening oxygenation is controversial, and several mechanisms have been proposed: (*1*) the dialyzer membrane interacts with the patient's blood, activating complement that causes leukoagglutination. These leukocyte-aggregates impact and are trapped in the pulmonary microvasculature, leading to V/Q mismatching and, possibly, interstitial edema (79). However, recent data tend to exclude leukagglutination as a major factor (80, 81). (*2*) CO_2 is lost to the atmosphere through the dialyzer membrane. This leads to a fall in arterial and mixed venous P_{CO_2}. To maintain tissue and blood CO_2 stores, the patient hypoventilates; this results in hypoxemia with a normal $A\text{-}a_{O_2}$ difference (80). (*3*) Some combination of these mechanisms, and (*4*) changes in V/Q relationships in the absence of leukocyte-trapping or hypoventilation. This mechanism was proposed by Jones and associates (77), who found a fall in Pa_{O_2} in a group of mechanically ventilated patients with an unchanging V_E during hemodialysis.

A multitude of *medications* frequently used in the ICU setting can impair oxygenation. Bronchodilators, such as intravenously administered aminophylline, inhaled salbutamol and isoproterenol, reverse large and small airway bronchoconstriction. They also possess inotropic and vasodilator properties and can increase perfusion to poorly ventilated lung units, resulting in V/Q mismatch and worsening hypoxemia (82–86). In some patients, although V/Q mismatch may worsen after bronchodilator treatment, the increased $P\bar{v}_{O_2}$ associated with an increased cardiac output may actually increase the Pa_{O_2} (9, 10). However, as many as 50% of asthmatic patients may experience a sustained (as long as 40 min) fall in Pa_{O_2} after successful treatment of their bronchoconstriction (82). Pretreatment pulmonary function findings in patients who experience post-treatment hypoxemia are similar to those patients whose Pa_{O_2} remains the same or increases (82). Some investigators have found that patients with the lowest baseline Pa_{O_2} either have a very small or no fall in Pa_{O_2} after treatment (84).

Many vasodilators are associated with a fall in Pa_{O_2} (82–107). Nitroprusside, intravenous nitroglycerin, and minoxidil administration in an animal model (oleic acid infusion) of ARDS is associated with a 20% fall in Pa_{O_2}; however, tissue oxygenation is maintained because cardiac output increases (90, 92, 100, 102). In humans, sublingual nitroglycerin, nitroprusside, nifedipine, and phentolamine have all been associated with post-treatment hypoxemia. The cause(s) of vasodilator-induced hypoxemia is unclear (table 5).

TABLE 5

PROPOSED CAUSES OF VASODILATOR-INDUCED HYPOXEMIA

1. Changes in distribution of pulmonary blood flow secondary to drug-induced increases in cardiac output
2. Relief of hypoxic pulmonary vasoconstriction as mixed venous O_2 increases
3. Inhibition of hypoxic vasoconstriction by the drugs themselves, particularly by calcium antagonists
4. Increases and decreases in intracardiac and pulmonary artery pressures, leading to redistribution of pulmonary blood flow
5. Direct action of drugs on pulmonary vascular tone

In contrast to the above drugs, hydralazine is associated with an increase in Pa_{O_2} in patients with left ventricular failure and cor pulmonale (87). Similarly, in an animal model of ARDS (i.e., oleic acid infusion), hydralazine did not cause a fall in Pa_{O_2} (90). This may be because hydralazine does not reverse hypoxic pulmonary vasoconstriction, thus preserving more normal V/Q relationships.

Low-dose dopamine worsens V/Q relationships and also may decrease V_E through its depressant effect on the carotid body (108–112). The hypercapnic ventilatory response is blunted by 24 to 74% in subjects receiving 5 μg/kg/min of dopamine.

To obviate the expected hypoxemia, the patient's $F_{I_{O_2}}$ can be increased prior to the above-mentioned interventions, procedures, and administration of medications. Additionally, monitoring oxygenation with a pulse oximeter should be considered.

There are *miscellaneous* conditions that may be associated with altered oxygenation. Unreported or unrecognized hyperthermia can lead to spurious hypoxemia because the arterial blood gases are processed at a lower temperature on the blood gas machine and then not corrected for temperature. The Pa_{O_2} falls 7% for every 1° C increase in temperature above 38° C (113). Elevated white blood cell (greater than 100,000 cell/mm³) and platelet counts through continued metabolic activity can lower the P_{O_2} in the blood gas syringe (114). This has been termed "pseudohypoxemia" and has been reported secondary to leukemia and thrombocytosis. The mean fall in Pa_{O_2} after storage of arterial blood for 1 h at room temperature was approximately 16 mm Hg. In contrast, in normal control subjects, Pa_{O_2} fell approximately 5 mm Hg over the same time period. However, if the patient's arterial blood samples were kept in ice at 2° C for 1 h, there was only a small fall in Pa_{O_2}.

A low Pa_{O_2} has been reported in patients with delirium tremens and seizures (115). Extrapolating from this data, it seems likely that the Pa_{O_2} will fall in mechanically ventilated patients with the onset of delirium tremens.

Intravenous lipid administration may alter respiratory function particularly in patients with pre-existing lung disease (116–121). Patients with acute respiratory failure may experience arterial desaturation, a low D_{LCO} with an increase in

TABLE 6

SIGNS AND SYMPTOMS OF HYPOXEMIA AND HYPERCAPNIA

Hypoxemia
Muscular incoordination
Confusion
Loss of judgment
Extreme restlessness, combative behavior
Tachycardia
Mild hypertension
Peripheral vasoconstriction
Cyanosis
Bradycardia*
Bradyarrhythmias*
Hypotension*
Hypercapnia
Progressive somnolence
Disorientation
Mucosal, scleral, conjunctival hyperemia
Diaphoresis
Tachycardia
Hypertension

* Associated with severe hypoxemia.

shunt fraction and A-a_{O_2} differences (121). The Pa_{O_2} returns to baseline levels within 45 min after the lipid infusion is discontinued.

An Approach to the Rapid Detection of Impaired Oxygenation

Because hypoxemia itself and/or the underlying condition(s) responsible for it may be life-threatening, early detection and correction of these disorders is imperative. The following is one approach to this problem.

Impaired oxygenation may be suspected when the patient manifests symptoms and signs of hypoxemia and/or hypercapnia (table 6). Conversely, the patient may be asymptomatic, and a "routine" arterial blood gas reveals impaired oxygenation. In the emergent situation, the clinician must simultaneously search for the proximate cause leading to life-threatening hypoxemia and/or respiratory distress and initiate appropriate corrective action.

Airway, respiratory, and circulatory status is assessed immediately. Ventilator problems are circumvented by disconnecting the patient from the mechanical ventilator and initiating hand ventilation using a self-inflating bag delivering 100% oxygen through the ET tube. An adequate airway is assured first by addressing any ET tube malfunctions present. ET tube position and patency are rapidly evaluated by observing normal chest excursion and by auscultating for bilateral breath sounds. Malpositioning, obstruction, or cuff leaks are determined as discussed (see above). In particular, the presence of a tension pneumothorax must be determined; if present, immediate decompression is mandatory (see above).

Concomitant with this evaluation of the respiratory system is the emergent assessment of circulatory status and cardiac rhythm. Palpation of the carotid pulses and observation of monitored displays of systemic arterial pressure and cardiac rhythm provide immediate information. Subsequently, blood pressure should be measured with a sphygmomanometer, and an electrocardiogram should be obtained. Systemic hypotension should be corrected as quickly as possible by placing the patient in the Trendelenburg position, administering intravenous fluids and adding vasopressor drugs as necessary. Concurrently, causes of shock such as myocardial infarction, arrhythmias, cardiac tamponade, massive pulmonary embolus, sepsis, and gastrointestinal hemorrhage should be evaluated.

Once the patient's condition is stabilized, a systematic search for the underlying cause of the impaired oxygenation is undertaken. This includes evaluation of problems such as progression of the underlying disease process or a superimposed disorder, and/or problems related to interventions or medications as has been discussed. The initial emphasis is directed toward disorders that are most common, most easily corrected, and/or pose the greatest risk to the patient. In virtually all circumstances, a chest roentgenogram should be obtained to assess ET tube position and to search for evidence of new or progressive cardiopulmonary disease(s).

Summary

Hypoxemia or worsening oxygenation is a common problem in the ICU. Ventilator-related problems, patient-related problems, including progression of the underlying disease process or superimposed disorders, and interventions, procedures, and medications can all adversely affect the patient's oxygenation status. Each of these causes should be sought for in a rapid and expeditious manner and appropriate corrective actions taken.

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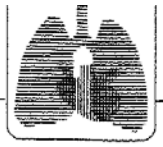

literature review

Top Ten List in Mechanical Ventilation*

Bruce P. Krieger, MD, FCCP

(CHEST 2002; 122:1797–1800)

Key words: ARDS; COPD; mechanical ventilation; noninvasive ventilation; sedation; weaning

Abbreviations: CPAP = continuous positive airway pressure; NIV = noninvasive ventilation; PEEP = positive end-expiratory pressure; PS = pressure support; V_T = tidal volume

Lung Protective Ventilation

1. The ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the ARDS. N Engl J Med 2000; 342:1301–1308

Data from animal studies in the 1970s and 1980s showed that ventilation with high tidal volume (V_T) levels was injurious to the lung. Approximately a decade ago, the concept of pressure-targeted, low V_T ventilation for patients with ARDS was born. A consensus conference report[1] on mechanical ventilation published in 1994 recommended this approach even though "permissive" hypercapnia often resulted from it.[2] However, it was not until the ARDS Network study was published that this recommendation was buttressed by evidence-based medicine. In this study, 361 patients were randomized to receive either a standard V_T (at 12 mL/kg predicted body weight) and a plateau pressure (measured after a 0.5-s pause at end inspiration) of ≤ 50 cm H_2O or a low V_T (at 6 mL/kg predicted body weight) with a plateau pressure of ≤ 30 cm H_2O. In the lower V_T group, the 28-day mortality rate was significantly lower than in the standard V_T group (31.0% vs 39.8%, respectively; $p = 0.007$), as was the number of days without the failure of nonpulmonary organs ($p = 0.006$) even though barotrauma was similar (10% vs 11%, respectively). This study therefore represents clinical confirmation that a lung protective ventilatory strategy for patients with ARDS is beneficial.

2. Richard NC, Maggiore SM, Jonson B, et al. Influence of tidal volume on alveolar recruitment: respective role of PEEP and a recruitment maneuver. Am J Respir Crit Care Med 2001; 163:1609–1613

Although the study by the ARDS Network showed a significant improvement in mortality when low V_T levels were used for ventilating patients with ARDS, smaller studies had previously failed to show statistical significance. Richard et al hypothesized that this inconsistency may have been due to alveolar derecruitment associated with reducing V_T from 10 to 6 mL/kg body weight. In their study of 15 patients with ARDS, volume differences between a pressure-volume curve that was recorded from 0 positive end-expiratory pressure (PEEP) vs a curve recorded from different PEEP levels were measured. The study demonstrated that the recruited volume and oxygenation were significantly lower when smaller V_T levels were used to ventilate these patients. However, the recruited volume was reestablished either after an increase in PEEP (by 4 cm H_2O) above the lower inflection point of the pressure-volume curve or by two sustained inflations at 45 cm of H_2O. Their study demonstrated a potential hazard of the lung-protective ventilatory strategy and corroborated previous observations that either periodic sighs (with the risk of alveolar overdistention) or high levels of PEEP may be necessary to optimize the benefits of the ARDS Network strategy. The ARDS Network is presently conducting a randomized study to clarify the optimal approach.

3. Crotti S, Mascheroni D, Caironi P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. Am J Respir Crit Care Med 2001; 164:131–140

A basic assumption of lung-protective ventilation is the concept of *open lung ventilation*, wherein the

*From the Division of Pulmonary and Critical Care Medicine, University of Miami School of Medicine at Mount Sinai Medical Center, Miami Beach, FL.

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Correspondence to: Bruce P. Krieger, MD, FCCP, Mount Sinai Medical Center, 4300 Alton Rd, Miami Beach, FL 33140; e-mail: BKriegermd@aol.com

pulmonary damage induced by recurrent alveolar collapse and reopening is minimized by adjusting PEEP, inspiratory time, and VT. Proof of this tenet has required extrapolation from the physiologic data. Two pioneers in this field (Drs. Gattinoni and Marini) collaborated in this study, and in an accompanying study of oleic acid-induced lung injury in animals,[3] to demonstrate recruitment utilizing quantitative analysis of CT images. Five patients with ARDS were studied at multiple combinations of inspiratory plateau pressures (10 to 45 cm H_2O) and PEEP levels (5 to 20 cm H_2O). Lung volume recruitment occurred over the entire spectrum of inspiration (independent of lower and upper inflection points), and progressively from nondependent to dependent lung regions. This study has provided direct evidence that end-expiratory collapse is dependent on the preceding inspiratory pressure and the superimposed pressure surrounding alveolar units during end-expiration. However, future studies with analyses of lung perfusion will be necessary to fully optimize lung-protective ventilatory techniques.

4. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001; 345: 568–573

Another lung-protective strategy that has been successfully utilized to improve oxygenation in mechanically ventilated patients with ARDS is accomplished by changing the patient from the supine position to the prone position. The mechanism for this improvement is hypothesized to be the result of improved and better distributed ventilation to the previously dependent areas of the lung. The Prone-Supine Study Group from Europe conducted a randomized, unblinded, controlled trial with a 6-month follow-up in 28 ICUs in Italy and 2 ICUs in Switzerland. One hundred fifty-two patients were allocated to prone positioning for ≥ 6 h per day for 10 days, while 152 patients were allocated to conventional (supine) positioning throughout their treatment. There was no difference in the 10-day mortality rate between the prone and the supine groups (21% vs 25%, respectively), at ICU discharge (51% vs 48%, respectively), or at the 6-month follow-up (63% vs 59%, respectively). This lack of significant improvement occurred despite significant ($p = 0.02$) increases in oxygenation in the prone group. This study has been criticized for using only 6 h of prone positioning. Therefore, two multi-institutional studies in Europe are presently underway to determine whether a more prolonged use of the prone position may improve mortality rates in ARDS patients, as has been suggested in smaller, uncontrolled series.

Noninvasive Ventilation

5. Vitacca M, Ambrosino N, Clini E, et al. Physiologic response to pressure support ventilation delivered before and after extubation in patients not capable of totally spontaneous autonomous breathing. Am J Respir Crit Care Med 2001; 164:638–641

Over the past 6 years, there has been a plethora of clinical articles showing the benefits of noninvasive ventilation (NIV). These results were extensively reviewed in a recent state-of-the-art article by Mehta and Hill.[4] NIV has been established as a preferred mode of ventilation during acute hypercapnic exacerbations of COPD.[5] Vitacca et al performed a physiologic study in 12 patients who were intubated because of hypercapnic respiratory failure due to COPD. Measurements included diaphragm energy expenditure (using esophageal and gastric balloons to record the pressure time product of the diaphragm), lung resistance and elastance, breathing pattern, dyspnea (as measured by a visual analog scale), and arterial blood gas measurements. The study also compared invasive pressure support (PS) ventilation to noninvasive PS ventilation. None of the patients were ready to sustain total spontaneous breathing. Both invasive and noninvasive PS ventilation resulted in similar reductions in diaphragm energy expenditure and improvements in arterial blood gas levels. However, noninvasive PS ventilation was better tolerated by patients, as determined by their dyspnea analysis. This study showed subjective advantages of noninvasive PS ventilation in patients with COPD. In addition, the data documented improvement in the pressure time product of the diaphragm compared to ventilation through a T-piece when PS was delivered noninvasively or via an endotracheal tube. The physiologic data in this article support the clinical recommendation that NIV be used as a bridge between mechanical ventilatory support and total spontaneous breathing in patients with hypercapnic ventilatory failure.[5]

Physiology and Overview

6. Tobin MJ. Advances in mechanical ventilation. N Engl J Med 2001; 344:1986–1996

This article is an update of Dr. Tobin's review of mechanical ventilation that was published in 1994 in the *New England Journal of Medicine*. It succinctly summarizes the significant changes that have occurred in the area of mechanical ventilation, including the interaction between the patient and the ventilator, lung-protective ventilation, and weaning. The review allows the clinician to appreciate the

[illegible] research, animal research, and the large, randomized, controlled clinical trials that have reshaped the intensivist's approach to diseases such as ARDS. This manuscript will remain the standard reference review article on mechanical ventilation for the next few years.

Weaning

7. Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000; 342:1471–1477

The transition from mechanical ventilator support to spontaneous breathing has traditionally been called *weaning*. Most efforts to expedite weaning have focused on manipulating and comparing different mechanical ventilatory modes. This sentinel article by Kress et al marks a conceptual change by linking a non-mechanical ventilation treatment that clinicians commonly use (sedation) to the weaning process. The authors conducted a randomized, controlled trial involving 128 adult patients who required infusions of sedative drugs (midazolam or propofol) because they were being mechanically ventilated. In 57 patients, the continuous infusion of sedative medication was interrupted on a daily basis to determine whether it was still required. If the researchers noted significant agitation after the withdrawal of sedation, the continuous IV infusions were restarted at half the previous dose. In a control group, the sedative infusions were interrupted at the discretion of the treating clinician. There was a significant decrease in the number of days of mechanical ventilation in the intervention group (4.9 vs 7.3 days, respectively; $p = 0.004$) as well as their length of stay in the ICUs ($p = 0.02$). There was no significant difference in complications, such as self-extubations. This article reminds clinicians that many "routine" aspects of critical care may affect the outcome of patients receiving mechanical ventilation.

8. MacIntyre NR, Cook DJ, Ely EW, et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest 2001; 120(suppl):375S–395S

The "Top 10 List in Mechanical Ventilation" would be incomplete without inclusion of this article from a *CHEST* supplement (December 2001), which was devoted to evidence-based guidelines for weaning and discontinuation of ventilatory support. This consensus is an exhaustive review of hundreds of studies involving weaning and highlights the heterogeneity, and often incompleteness, of many of these studies. The reference quoted is from section 1 ("Guidelines" section) and summarizes the consensus opinions of the task force that was facilitated by the American College of Chest Physicians, the American College of Critial Care Medicine, and the American Association for Respiratory Care. The article includes 12 recommendations, all of which are accompanied by the rationale for the recommendation and the scientific evidence supporting the recommendation. A reference list of 224 articles accompanies the article so that the reader may refer to the primary literature. This section is part of an exhaustive review of the literature that includes 11 other articles.

9. Vitacca M, Vianello A, Colombo D, et al. Comparison of two methods for weaning patients with COPD requiring mechanical ventilation for more than 15 days. Am J Respir Crit Care Med 2001; 164:225–230

Until approximately 8 years ago, weaning patients from mechanical ventilatory support was as much of an art as a science. Since then, large, randomized, multi-institutional studies have provided evidence that weaning time is prolonged when intermittent mandatory ventilation is used as the weaning mode[6,7] and that a 30-min trial of spontaneous breathing is as effective as 2-h trial to determine whether weaning will be successful.[8] However, these studies included patients with varying diagnoses. The article by Vitacca and coworkers focused on 52 patients who required mechanical ventilation because of an acute exacerbation of COPD. Half of these patients were weaned using continuous positive airway pressure (CPAP) from an initial PS setting of approximately 19 cm H_2O in 2-cm increments twice daily until they tolerated CPAP with a PS of 8 cm for 8 h. The remaining 26 patients were weaned by spontaneous breathing trials via a T-piece performed twice daily. Both groups achieved equal rates of weaning success (73% vs 77%, respectively), duration of ventilatory support (181 vs 130 h, respectively), and ICU lengths of stay. Therefore, in this select group of COPD patients, neither method appeared to be superior or inferior. The authors also compared the study patients (combined data) to 55 patients who were being managed without a formal protocol. In this comparison, the study patients whose conditions had been managed via a protocol were successfully weaned more frequently (87% vs 70%, respectively), and experienced shorter durations of mechanical ventila-

shorter stays in the ICU (27 vs 38 days, respectively) than the group of patients whose conditions had been managed without a protocol. Therefore, although there was no difference in weaning patients with COPD using CPAP and PS vs T-piece trials, there were significant benefits when a set protocol was utilized.

10. Scheinhorn DJ, Chao DC, Stearn-Hassenpflug MS, et al. Outcomes in post-ICU mechanical ventilation: a therapist-implemented weaning protocol. Chest 2001; 119:236–242

Approximately 20% of patients fail to wean from mechanical ventilation in the ICU and are eventually transferred to alternative settings for continued care (*ie*, long-term acute care facilities). Strategies for weaning that are applicable to the acute care setting are not necessarily designed for long-term facilities. Therefore, the article by Scheinhorn and associates at the Barlow Respiratory Hospital is very pertinent to this group of patients. The investigators reported the results of treating 271 consecutive patients who had been admitted for weaning to their long-term facility during an 18-month period and compared them to a group of 238 patients who had been treated at the same facility by the same physicians for the previous 2 years. The patients were managed by a therapist-implemented, patient-specific weaning protocol that was detailed in the article. Compared to the control subjects, the protocol patients weaned significantly faster (17 vs 29 days, respectively; $p < 0.001$). There were no differences in other outcomes such as weaning success (55% vs 58%, respectively), mortality rate (27% vs 31%, respectively), or patients who remained ventilator-dependent (18% vs 11%, respectively). This article is important because it documented the outcomes of patients in long-term facilities and described a successful respiratory therapy-driven protocol that resulted in improved outcomes.

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Acute Respiratory Distress Syndrome (ARDS)

Review Articles

Medical Progress

The Acute Respiratory Distress Syndrome

Lorraine B. Ware, M.D., and Michael A. Matthay, M.D.

THE acute respiratory distress syndrome is a common, devastating clinical syndrome of acute lung injury that affects both medical and surgical patients. Since the last review of this syndrome appeared in the *Journal*,[1] more uniform definitions have been devised and important advances have occurred in the understanding of the epidemiology, natural history, and pathogenesis of the disease, leading to the design and testing of new treatment strategies. This article provides an overview of the definitions, clinical features, and epidemiology of the acute respiratory distress syndrome and discusses advances in the areas of pathogenesis, resolution, and treatment.

HISTORICAL PERSPECTIVE AND DEFINITIONS

The first description of acute respiratory distress syndrome appeared in 1967, when Ashbaugh and colleagues described 12 patients with acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance, and diffuse infiltrates evident on the chest radiograph.[2] Initially called the adult respiratory distress syndrome,[3] this entity is now termed the acute respiratory distress syndrome, since it does occur in children. Because the initial definition lacks specific criteria that could be used to identify patients systematically, there was controversy over the incidence and natural history of the syndrome and the mortality associated with it. In 1988, an expanded definition was proposed that quantified the physiologic respiratory impairment through the use of a four-point lung-injury scoring system that was based on the level of positive end-expiratory pressure, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, the static lung compliance, and the degree of infiltration evident on chest radiographs.[4] Other factors included in the assessment were the inciting clinical disorder and the presence or absence of nonpulmonary organ dysfunction (Table 1). Although the lung-injury scoring system has been widely used to quantify the severity of lung injury in both clinical research and clinical trials, it cannot be used to predict the outcome during the first 24 to 72 hours after the onset of the acute respiratory distress syndrome and thus has limited clinical usefulness.[4-7] When the scoring system is used four to seven days after the onset of the syndrome, scores of 2.5 or higher may be predictive of a complicated course with the need for prolonged mechanical ventilation.[8]

In 1994, a new definition was recommended by the American–European Consensus Conference Committee (Table 1).[5] The consensus definition has two advantages. First, it recognizes that the severity of clinical lung injury varies: patients with less severe hypoxemia (as defined by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of 300 or less) are considered to have acute lung injury, and those with more severe hypoxemia (as defined by a ratio of 200 or less) are considered to have the acute respiratory distress syndrome. The recognition of patients with acute lung injury may facilitate earlier enrollment of affected patients in clinical trials. Second, the definition is simple to apply in the clinical setting. However, this simplicity is also a disadvantage, since factors that influence the outcome, such as the underlying cause and whether other organ systems are affected, do not need to be assessed.[4,7,9-11] In addition, the criterion for the presence of bilateral infiltrates on chest radiography consistent with the presence of pulmonary edema is not sufficiently specific to be applied consistently by experienced clinicians.[12,13] Nevertheless, the widespread acceptance of both the 1994 consensus definition and the 1988 lung-injury scoring system has improved the standardization of clinical research and trials. We recommend that clinicians routinely use the 1994 consensus definition to allow comparison of their patients with patients enrolled in clinical trials.

CLINICAL, PATHOLOGICAL, AND RADIOGRAPHIC FEATURES

The definitions discussed above identify patients early in the course of acute lung injury and the acute respiratory distress syndrome. However, the syndrome

From the Cardiovascular Research Institute (L.B.W., M.A.M.) and the Departments of Medicine (L.B.W., M.A.M.) and Anesthesia (M.A.M.), University of California, San Francisco, San Francisco. Address reprint requests to Dr. Matthay at CVRI, Box 0130, 505 Parnassus Ave., University of California, San Francisco, San Francisco, CA 94143-0130, or at matthay@itsa.ucsf.edu.

TABLE 1. DEFINITIONS OF THE ACUTE RESPIRATORY DISTRESS SYNDROME.*

REFERENCE	YEAR	DEFINITION OR CRITERIA	ADVANTAGES	DISADVANTAGES
Petty and Ashbaugh[2]	1971	Severe dyspnea, tachypnea Cyanosis refractory to oxygen therapy Decreased pulmonary compliance Diffuse alveolar infiltrates on chest radiography Atelectasis, vascular congestion, hemorrhage, pulmonary edema, and hyaline membranes at autopsy	Pure description Summarizes clinical features well	Lacks specific criteria to identify patients systematically
Murray et al.[3]	1988	Precipitating direct or indirect lung injury Mild to moderate or severe lung injury Nonpulmonary organ dysfunction	Includes 4 point lung injury scoring system Specifies clinical cause of lung injury Includes consideration of the presence or absence of systemic disease	Lung injury score not predictive of outcome Lacks specific criteria to exclude a diagnosis of cardiogenic pulmonary edema
Bernard et al.[4]	1994	Acute onset Bilateral infiltrates on chest radiography Pulmonary artery wedge pressure ≤18 mm Hg or the absence of clinical evidence of left atrial hypertension Acute lung injury considered to be present if PaO_2/FIO_2 is ≤200 Acute respiratory distress syndrome considered to be present if PaO_2/FIO_2 is ≤200	Simple, easy to use, especially in clinical trials Recognizes the spectrum of the clinical disorder	Does not specify cause Does not consider the presence or absence of multiorgan dysfunction Radiographic findings not specific

*PaO_2 denotes partial pressure of arterial oxygen, and FIO_2 fraction of inspired oxygen.

is often progressive, characterized by distinct stages with different clinical, histopathological, and radiographic manifestations. The acute, or exudative, phase is manifested by the rapid onset of respiratory failure in a patient with a risk factor for the condition. Arterial hypoxemia that is refractory to treatment with supplemental oxygen is a characteristic feature. Radiographically, the findings are indistinguishable from those of cardiogenic pulmonary edema.[14] Bilateral infiltrates may be patchy or asymmetric and may include pleural effusions (Fig. 1).[15] Computed tomographic scanning has demonstrated that alveolar filling, consolidation, and atelectasis occur predominantly in dependent lung zones, whereas other areas may be relatively spared (Fig. 1).[16,17] However, bronchoalveolar lavage studies indicate that even radiographically spared, nondependent areas may have substantial inflammation.[18] Pathological findings include diffuse alveolar damage, with neutrophils, macrophages, erythrocytes, hyaline membranes, and protein-rich edema fluid in the alveolar spaces;[19] capillary injury, and disruption of the alveolar epithelium (Fig. 2).[20-22]

Although acute lung injury and the acute respiratory distress syndrome may resolve completely in some patients after the acute phase, in others it progresses to fibrosing alveolitis with persistent hypoxemia, increased alveolar dead space, and a further decrease in pulmonary compliance.[20,23] Pulmonary hypertension, owing to obliteration of the pulmonary-capillary bed, may be severe and may lead to right ventricular failure.[23] Chest radiographs show linear opacities, consistent with the presence of evolving fibrosis (Fig. 1). Pneumothorax may occur,[24] but the incidence is only 10 to 13 percent and is not clearly related to airway pressures or the level of positive end-expiratory pressure.[25] Computed tomography of the chest shows diffuse interstitial opacities and bullae (Fig. 1).[17] Histologically, there is fibrosis along with acute and chronic inflammatory cells and partial resolution of the pulmonary edema (Fig. 2).[19,21]

The recovery phase is characterized by the gradual resolution of hypoxemia and improved lung compliance. Typically, the radiographic abnormalities resolve completely. The degree of histologic resolution of fibrosis has not been well characterized, although in many patients pulmonary function returns to normal.

EPIDEMIOLOGY

Incidence

An accurate estimation of the incidence of acute lung injury and the acute respiratory distress syndrome has been hindered by the lack of a uniform definition and the heterogeneity of the causes and clinical manifestations. An early estimate by the National Institutes of Health (NIH) suggested that the annual incidence in the United States was 75 per 100,000 population.[26] More recent studies reported lower incidences of 1.5 to 8.3 per 100,000.[27-29] However, the first epidemiologic study to use the 1994 consensus definition reported considerably higher annual incidences in Scandinavia: 17.9 per 100,000 for acute lung injury and 13.5 per 100,000 for the acute

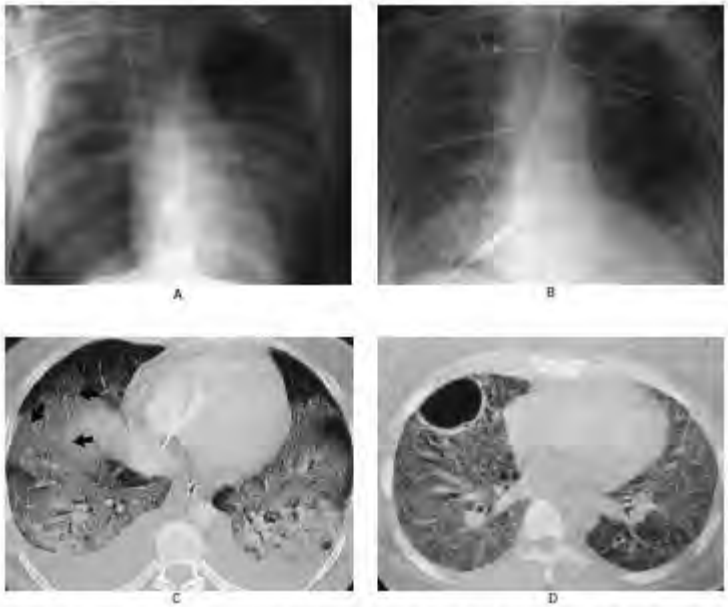

Figure 1. Radiographic and Computed Tomographic (CT) Findings in the Acute, or Exudative, Phase (Panels A and C) and the Fibrosing-Alveolitis Phase (Panels B and D) of Acute Lung Injury and the Acute Respiratory Distress Syndrome.

Panel A shows an anteroposterior chest radiograph from a 42-year-old man with the acute respiratory distress syndrome associated with gram-negative sepsis who was receiving mechanical ventilation. The pulmonary-artery wedge pressure, measured with a pulmonary-artery catheter, was 4 mm Hg. There are diffuse bilateral alveolar opacities consistent with the presence of pulmonary edema. Panel B shows an anteroposterior chest radiograph from a 60-year-old man with acute lung injury and the acute respiratory distress syndrome who had been receiving mechanical ventilation for seven days. Reticular opacities are present throughout both lung fields, a finding suggestive of the development of fibrosing alveolitis. Panel C shows a CT scan of the chest obtained during the acute phase. The bilateral alveolar opacities are denser in the dependent, posterior lung zones, with sparing of the anterior lung fields. The arrows indicate thickened interlobular septa, consistent with the presence of pulmonary edema. The bilateral pleural effusions are a common finding.[16,17] Panel D shows a CT scan of the chest obtained during the fibrosing-alveolitis phase. There are reticular opacities and diffuse ground-glass opacities throughout both lung fields, and a large bulla is present in the left anterior hemithorax. Panels C and D are reprinted from Goodman[16] with the permission of the publisher.

respiratory distress syndrome.[10] On the basis of the results of screening of large numbers of patients by the NIH Acute Respiratory Distress Syndrome Network over the past three years, some investigators believe that the original estimate of 75 per 100,000 per year may be accurate. To settle this issue, a prospective epidemiologic study that is using the 1994 consensus definition is under way in Seattle.

Clinical Disorders and Risk Factors

The ability to identify patients at risk for acute lung injury and the acute respiratory distress syndrome is important if therapies are to be developed to prevent the disorder. The commonly associated clinical disorders can be divided into those associated with direct injury to the lung and those that cause indirect lung injury in the setting of a systemic process (Ta-

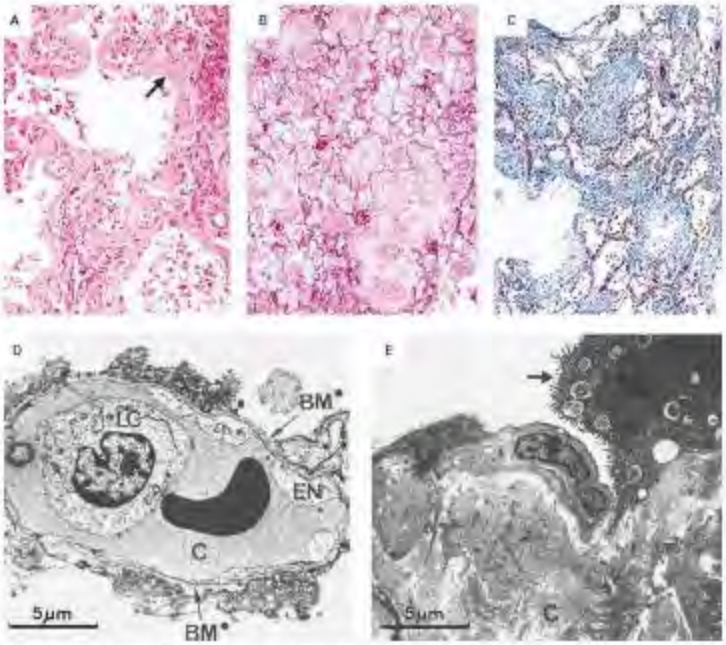

Figure 2. Findings on Light Microscopy and Electron Microscopy during the Acute Phase (Panels A and D) and the Fibrosing-Alveolitis Phase (Panels B, C, and E) of Acute Lung Injury and the Acute Respiratory Distress Syndrome.

Panel A shows a lung-biopsy specimen obtained from a patient two days after the onset of the syndrome as a result of the aspiration of gastric contents. Characteristic hyaline membranes are evident (arrow), with associated intraalveolar red cells and neutrophils, findings that are consistent with the pathological diagnosis of diffuse alveolar damage (hematoxylin and eosin, ×30). Panels B and C show lung-biopsy specimens obtained 14 days after the onset of sepsis-associated acute lung injury and the acute respiratory distress syndrome. Panel B shows granulation tissue in the distal air spaces with a chronic inflammatory-cell infiltrate (hematoxylin and eosin, ×60). Trichrome staining in Panel C reveals collagen deposition (dark blue areas) in the granulation tissue, a finding that is consistent with the deposition of extracellular matrix in the alveolar compartment (×60). Panel D shows a specimen of lung tissue from a patient who died four days after the onset of acute lung injury and the acute respiratory distress syndrome; there is injury to both the capillary endothelium and the alveolar epithelium. There is an intravascular neutrophil (LC) in the capillary (C). Vacuolization and swelling of the endothelium (EN) are apparent. Loss of alveolar epithelial cells is also apparent, with the formation of hyaline membranes on the epithelial side of the basement membrane (BM*). Panel E shows a specimen of lung tissue obtained from a patient during the fibrosing-alveolitis phase in which there is evidence of reepithelialization of the epithelial barrier with alveolar epithelial type II cells. The arrow indicates a typical type II cell with microvilli and lamellar bodies containing surfactant. The epithelial cell immediately adjacent to this cell is in the process of changing to a type I cell, with flattening, loss of lamellar bodies, and microvilli. The interstitium is thickened, with deposition of collagen (C). Panels A, B, and C were supplied by Dr. Martha Warnock. Panel D was reprinted from Bachofen and Weibel[36] with the permission of the publisher. Panel E was reprinted from Anderson and Thiele[37] with the permission of the publisher.

ble 2).[6,9,15,33] Overall, sepsis is associated with the highest risk of progression to acute lung injury or the acute respiratory distress syndrome, approximately 40 percent.[31,33] The presence of multiple predisposing disorders substantially increases the risk,[31] as does the presence of secondary factors including chronic alcohol abuse,[33,34] chronic lung disease,[32] and a low serum pH.[33]

Outcomes

Until recently, most studies of acute lung injury and the acute respiratory distress syndrome have reported a mortality rate of 40 to 60 percent.[6,7,9,32,35-38] The majority of deaths are attributable to sepsis or multiorgan dysfunction rather than primary respiratory causes,[6,7,9,10,34] although the recent therapeutic success of ventilation with low tidal volumes indicates that in some cases death is directly related to lung injury. Two reports suggest that mortality from this disease may be decreasing. The first, from a large county hospital in Seattle, found that the mortality rate was 36 percent in 1993 as compared with rates of 53 to 68 percent in the period from 1983 to 1987.[38] The second, from a hospital in the United Kingdom, reported a decline in the mortality rate from 66 percent to 34 percent between 1990 to 1993 and 1994 to 1997.[39] Possible explanations for the decrease include more effective treatments for sepsis, changes in the method of mechanical ventilation, and improvements in the supportive care of critically ill patients. The possibility that mortality is decreasing emphasizes the importance of the use of randomized control subjects rather than historical controls in clinical studies of the disorder.

Factors whose presence can be used to predict the risk of death at the time of diagnosis of acute lung injury and the acute respiratory distress syndrome include chronic liver disease, nonpulmonary organ dysfunction, sepsis, and advanced age.[6,7,10,30] Surprisingly, initial indexes of oxygenation and ventilation, including the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen and the lung-injury score, do not predict outcome. In three large studies, the mortality rate among patients with an initial ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of 300 or less was similar to that among patients with a ratio of 200 or less.[6,7,30] However, the failure of pulmonary function to improve during the first week of treatment is a negative prognostic factor.[8]

In most patients who survive, pulmonary function returns nearly to normal within 6 to 12 months, despite the severe injury to the lung.[40] Residual impairments of pulmonary mechanics may include mild restriction, obstruction, impairment of the diffusing capacity for carbon monoxide, or gas-exchange abnormalities with exercise, but these abnormalities are usually asymptomatic.[41,42] Severe disease and prolonged mechanical ventilation identify patients at highest risk for persistent abnormalities of pulmonary function.[42,43] Those who survive the illness have a reduced health-related quality of life as well as pulmonary-disease–specific health-related quality of life.[42,44-46]

TABLE 2. CLINICAL DISORDERS ASSOCIATED WITH THE DEVELOPMENT OF THE ACUTE RESPIRATORY DISTRESS SYNDROME.

DIRECT LUNG INJURY	INDIRECT LUNG INJURY
Common causes	*Common causes*
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with shock and multiple transfusions
Less common causes	*Less common causes*
Pulmonary contusion	Cardiopulmonary bypass
Fat emboli	Drug overdose
Near drowning	Acute pancreatitis
Inhalational injury	Transfusions of blood products
Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy	

PATHOGENESIS

Endothelial and Epithelial Injury

Two separate barriers form the alveolar–capillary barrier, the microvascular endothelium and the alveolar epithelium (Fig. 3). The acute phase of acute lung injury and the acute respiratory distress syndrome is characterized by the influx of protein-rich edema fluid into the air spaces as a consequence of increased permeability of the alveolar–capillary barrier.[47] The importance of endothelial injury and increased vascular permeability to the formation of pulmonary edema in this disorder has been well established.

The critical importance of epithelial injury to both the development of and recovery from the disorder has become better recognized.[18,22,48] The degree of alveolar epithelial injury is an important predictor of the outcome.[49,50] The normal alveolar epithelium is composed of two types of cells (Fig. 3). Flat type I cells make up 90 percent of the alveolar surface area and are easily injured. Cuboidal type II cells make up the remaining 10 percent of the alveolar surface area and are more resistant to injury; their functions include surfactant production, ion transport, and proliferation and differentiation to type I cells after injury.

The loss of epithelial integrity in acute lung injury and the acute respiratory distress syndrome has a number of consequences. First, under normal conditions, the epithelial barrier is much less permeable than the endothelial barrier.[48] Thus, epithelial injury can contribute to alveolar flooding. Second, the loss of epithelial integrity and injury to type II cells disrupt normal epithelial fluid transport, impairing the re-

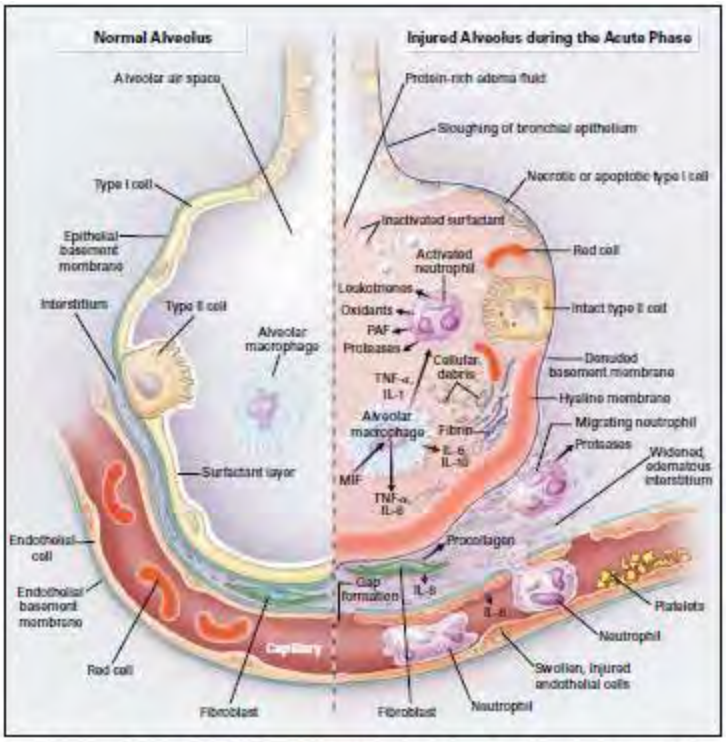

Figure 3. The Normal Alveolus (Left-Hand Side) and the Injured Alveolus in the Acute Phase of Acute Lung Injury and the Acute Respiratory Distress Syndrome (Right-Hand Side).

In the acute phase of the syndrome (right-hand side), there is sloughing of both the bronchial and alveolar epithelial cells, with the formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils are shown adhering to the injured capillary endothelium and marginating through the interstitium into the air space, which is filled with protein-rich edema fluid. In the air space, an alveolar macrophage is secreting cytokines, interleukin-1, 6, 8, and 10, IL-1, 6, 8, and 10 and tumor necrosis factor α (TNF-α), which act locally to stimulate chemotaxis and activate neutrophils. Macrophages also secrete other cytokines, including interleukin-1, 8, and 10. Interleukin-1 can also stimulate the production of extracellular matrix by fibroblasts. Neutrophils can release oxidants, proteases, leukotrienes, and other proinflammatory molecules, such as platelet-activating factor (PAF). A number of anti-inflammatory mediators are also present in the alveolar milieu, including interleukin-1–receptor antagonist, soluble tumor necrosis factor receptor, autoantibodies against interleukin-8, and cytokines such as interleukin-10 and 11 (not shown). The influx of protein-rich edema fluid into the alveolus has led to the inactivation of surfactant. MIF denotes macrophage inhibitory factor.

moval of edema fluid from the alveolar space.[31,32] Third, injury to type II cells reduces the production and turnover of surfactant,[33] contributing to the characteristic surfactant abnormalities.[34,35] Fourth, loss of the epithelial barrier can lead to septic shock in patients with bacterial pneumonia.[36] Finally, if injury to the alveolar epithelium is severe, disorganized or insufficient epithelial repair may lead to fibrosis.[37]

Neutrophil-Dependent Lung Injury

Clinical and experimental studies have provided circumstantial evidence of the occurrence of neutrophil-mediated injury in acute lung injury and the acute respiratory distress syndrome. Histologic studies of lung specimens obtained early in the course of the disorder show a marked accumulation of neutrophils.[20,21] Neutrophils predominate in the pulmonary edema fluid and bronchoalveolar-lavage fluid obtained from affected patients,[38] and many animal models of acute lung injury are neutrophil-dependent.[38,39] Some of the mechanisms of the sequestration and activation of neutrophils and of neutrophil-mediated lung injury are summarized in Figure 3.

New evidence raises the question of whether neutrophilic inflammation is the cause or the result of lung injury. Acute lung injury and the acute respiratory distress syndrome may develop in patients with profound neutropenia,[40] and some animal models of acute lung injury are neutrophil-independent. In clinical trials in which patients with severe pneumonia received granulocyte colony-stimulating factor in order to increase the number of circulating neutrophils, the incidence or severity of lung injury did not increase.[41] The neutrophil has a critical role in host defense in this disorder, a factor that may explain, in part, why antiinflammatory strategies have largely been unsuccessful.

Other Proinflammatory Mechanisms

Cytokines

A complex network of cytokines and other proinflammatory compounds initiate and amplify the inflammatory response in acute lung injury and the acute respiratory distress syndrome (Fig. 3). Proinflammatory cytokines may be produced locally in the lung by inflammatory cells, lung epithelial cells, or fibroblasts. The regulation of cytokine production by extrapulmonary factors has also been described. Macrophage inhibitory factor is a regulatory cytokine produced by the anterior pituitary that is found in high concentrations in the bronchoalveolar-lavage fluid of patients with the syndrome.[42] This cytokine increases production of the proinflammatory cytokines interleukin-8 and tumor necrosis factor α and can override glucocorticoid-mediated inhibition of cytokine secretion.

New evidence indicates that it is not only the production of proinflammatory cytokines that is important, but also the balance between proinflammatory and antiinflammatory mediators. Several endogenous inhibitors of proinflammatory cytokines have been described, including interleukin-1–receptor antagonist, soluble tumor necrosis factor receptor, autoantibodies against interleukin-8, and antiinflammatory cytokines such as interleukin-10 and 11.[38,43] Better understanding of the role of cytokines in acute lung injury and the acute respiratory distress syndrome will be gained through studies of the biologic activity of specific cytokines,[43,44] rather than by an assessment of static levels by immunologic methods.

Ventilator-Induced Lung Injury

Older studies focused on the potential toxic effects of high fractions of inspired oxygen,[29] but experimental evidence indicates that mechanical ventilation at high volumes and pressures can injure the lung,[45] causing increased permeability pulmonary edema in the uninjured lung[45,46] and enhanced edema in the injured lung.[47] Initial theories formulated to explain these deleterious effects focused on capillary stress failure due to alveolar overdistention. More recently, cyclic opening and closing of atelectatic alveoli during mechanical ventilation have been shown to cause lung injury independently of alveolar overdistention. Alveolar overdistention coupled with the repeated collapse and reopening of alveoli can initiate a cascade of proinflammatory cytokines.[48]

In patients with acute lung injury and the acute respiratory distress syndrome, ventilation at traditional tidal volumes (10 to 15 ml per kilogram of predicted body weight) may overdistend uninjured alveoli, perhaps promoting further lung injury, inhibiting resolution of the disorder, and contributing to multiorgan failure.[48] The failure of traditional ventilatory strategies to prevent end-expiratory closure of atelectatic alveoli may also contribute to lung injury. These issues have led to a number of clinical trials of protective ventilatory strategies to reduce alveolar overdistention and increase the recruitment of atelectatic alveoli. Interestingly, a recent study found that a strategy of protective ventilation could reduce both the pulmonary and the systemic cytokine response.[48]

Other Mechanisms of Injury

Like any form of inflammation, acute lung injury and the acute respiratory distress syndrome represent a complex process in which multiple pathways can propagate or inhibit lung injury.[18,19] For example, abnormalities of the coagulation system often develop, leading to platelet–fibrin thrombi in small vessels and impaired fibrinolysis within the distal air spaces of the injured lung.[18,19] Also, abnormalities in the production, composition, and function of surfactant probably contribute to alveolar collapse and gas-exchange abnormalities.[34,35]

Fibrosing Alveolitis

After the acute phase of acute lung injury and the acute respiratory distress syndrome, some patients have an uncomplicated course and rapid resolution of the disorder.[69,70,71] Others have progression to fibrotic lung injury, and such injury can be observed histologically as early as five to seven days after the onset of the disorder.[18,20,22] The alveolar space becomes filled with mesenchymal cells and their products, along with new blood vessels (Fig. 2).[72] The finding of fibrosing alveolitis on histologic analysis correlates with an increased risk of death,[73] and patients who die of the condition have a marked accumulation of collagen and fibronectin in the lung at autopsy.[74]

The process of fibrosing alveolitis apparently begins early in the course of the disorder and may be promoted by early proinflammatory mediators such as interleukin-1.[75,76] Levels of procollagen III peptide, a precursor of collagen synthesis, are elevated in the alveolar compartment very early in the course of the illness, even at the time of intubation and the initiation of mechanical ventilation.[77,78] Furthermore, the early appearance of procollagen III in the alveolar space is associated with an increased risk of death.[77,78]

RESOLUTION

Strategies that hasten the resolution of the illness may ultimately be as important as those that attenuate early inflammatory lung injury. Alveolar edema is resolved by the active transport of sodium and perhaps chloride from the distal air spaces into the lung interstitium (Fig. 4).[79-83] Water follows passively, probably through transcellular water channels, the aquaporins, located primarily on type I cells.[82,84] In clinical studies, clearance of alveolar fluid can occur surprisingly early and is often apparent within the first few hours after intubation and the initiation of mechanical ventilation.[69,70,71] Maintenance of the ability to remove alveolar fluid is associated with improved oxygenation, a shorter duration of mechanical ventilation, and an increased likelihood of survival.[69,70]

A considerable quantity of both soluble and insoluble protein must also be removed from the air spaces. The removal of insoluble protein is particularly important, since hyaline membranes provide a framework for the growth of fibrous tissue.[67] Soluble protein appears to be removed primarily by diffusion between alveolar epithelial cells. Insoluble protein may be removed by endocytosis and transcytosis by alveolar epithelial cells and by phagocytosis by macrophages (Fig. 4).[85]

The alveolar epithelial type II cell is the progenitor for reepithelialization of a denuded alveolar epithelium. Type II cells proliferate to cover the denuded basement membrane and then differentiate into type I cells, restoring the normal alveolar architecture and increasing the fluid-transport capacity of the alveolar epithelium.[86] This proliferation is controlled by epithelial growth factors, including keratinocyte and hepatocyte growth factors.

The mechanisms underlying the resolution of the inflammatory-cell infiltrate and fibrosis are unclear. Apoptosis (programmed cell death) is thought to be a major mechanism for the clearance of neutrophils from sites of inflammation and may be important in the clearance of neutrophils from the injured lung. However, in one study of bronchoalveolar-lavage fluid from patients with acute lung injury and the acute respiratory distress syndrome, the numbers of apoptotic neutrophils were low, perhaps because of the presence of antiapoptotic factors such as granulocyte colony-stimulating factor and granulocyte–macrophage colony-stimulating factor.[87] Nevertheless, high concentrations of the markers of apoptosis are present in the pulmonary edema fluid of patients,[88] and exposure in vitro to bronchoalveolar-lavage fluids from these patients can promote epithelial-cell apoptosis.[89,90] These are potentially important observations, since the mechanisms that alter epithelial integrity need to be identified. The role of proapoptotic and antiapoptotic mechanisms in both the injury and repair of the alveolar epithelium and the lung endothelium is an important area for future research.

TREATMENT

Approach to Treatment

Improvement in the supportive care of patients with acute lung injury and the acute respiratory distress syndrome may have contributed to the recent decline in the mortality rate.[36,37] There should be a careful search for the underlying cause, with particular attention paid to the possibility of treatable infections such as sepsis or pneumonia. Abdominal infections should be treated promptly with antimicrobial agents or surgery. Prevention or early treatment of nosocomial infections is critical, since patients frequently die of uncontrolled infection.[36,37] Adequate nutrition through the use of enteral feeding is preferred to parenteral nutrition since this route does not carry the serious risk of catheter-induced sepsis.[91] Prevention of gastrointestinal bleeding and thromboembolism is also important.[92]

An improved understanding of the pathogenesis of acute lung injury and the acute respiratory distress syndrome has led to the assessment of several novel treatment strategies. Although many specific therapies have not proved beneficial, it is encouraging that the quality of clinical trials is improving. An important advance has been the establishment of a network supported by the NIH that includes 10 centers, 24 hospitals, and 75 intensive care units and that provides the infrastructure for well-designed, multicenter, randomized trials of potential new therapies.

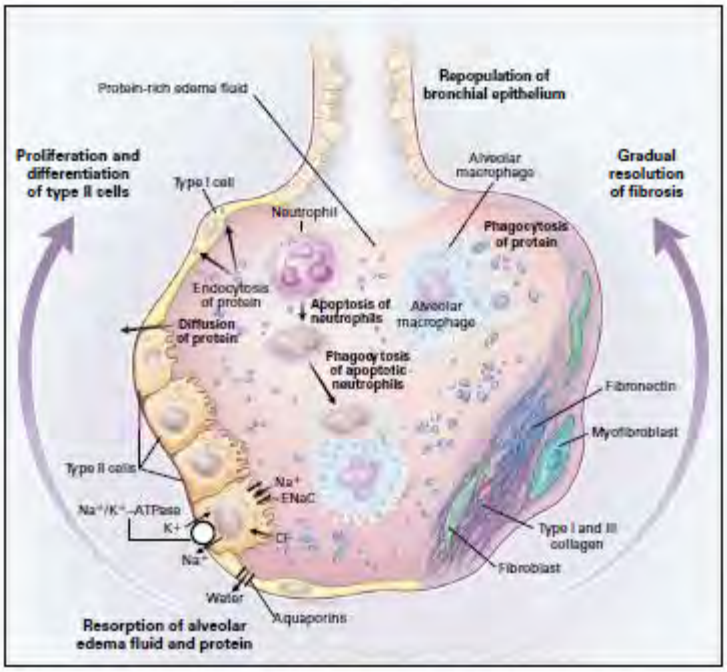

Figure 4. Mechanisms Important in the Resolution of Acute Lung Injury and the Acute Respiratory Distress Syndrome.
On the left side of the alveolus, the alveolar epithelium is being repopulated by the proliferation and differentiation of alveolar type II cells. Resorption of alveolar edema fluid is shown at the base of the alveolus, with sodium and chloride being transported through the apical membrane of type II cells by the sodium pump (Na+/K+–ATPase). The relevant pathways for chloride transport are unclear. Water is shown moving through water channels, the aquaporins, located primarily on type I cells. Some water may also cross by a paracellular route. Soluble protein is probably cleared primarily by paracellular diffusion and secondarily by endocytosis by alveolar epithelial cells. Macrophages remove insoluble protein and apoptotic neutrophils by phagocytosis. On the right side of the alveolus, the gradual remodeling and resolution of intraalveolar and interstitial granulation tissue and fibrosis are shown.

Mechanical Ventilation

The most appropriate method of mechanical ventilation in the acute respiratory distress syndrome has been controversial since the syndrome was first described. Although the tidal volume in normal persons at rest is 6 to 7 ml per kilogram, historically a volume of 12 to 15 ml per kilogram was recommended in patients with acute lung injury and the acute respiratory distress syndrome. This comparatively high tidal volume may cause further lung injury. Interestingly, the possibility of ventilator-associated lung injury was first considered in the 1970s,[54] leading to a

study of extracorporeal membrane oxygenation in which the tidal volume was reduced to 8 to 9 ml per kilogram.[92] However, this strategy, like extracorporeal removal of carbon dioxide in a subsequent study, failed to decrease mortality (Table 3).[93]

As described in this issue of the *Journal*, the NIH Acute Respiratory Distress Syndrome Network compared a traditional tidal volume (12 ml per kilogram of predicted body weight) with a lower tidal volume (6 ml per kilogram of predicted body weight) in 861 patients.[10a] In the group receiving lower tidal volumes, plateau pressure (airway pressure measured after a 0.5-second pause at the end of inspiration) could not exceed 30 cm of water and a detailed protocol was used to adjust the fraction of inspired oxygen and positive end-expiratory pressure. The in-hospital mortality rate was 39.8 percent in the group treated with traditional tidal volumes and 31.0 percent in the group treated with lower tidal volumes ($P=0.007$). Thus, mortality was reduced by 22 percent in the group treated with lower tidal volumes, a finding of major importance. This large multicenter trial provides convincing evidence that a specific therapy for the acute respiratory distress syndrome can reduce mortality. It also provides evidence of the clinical significance of ventilator-associated lung injury and provides a well-defined protocol for ventilation against which future strategies can be compared.

The positive results of this trial differed from those of two previous studies of low tidal volumes, a Canadian study of 120 patients[10b] and a European study of 116 patients.[10c] There are several possible explanations for the discrepant results. First, the NIH study had the lowest tidal volume when the tidal volumes were compared with the use of the same calculation of ideal body weight. Thus, the NIH study may have been better able to show a difference between the treatment groups. Second, the study treated respiratory acidosis associated with alveolar hypoventilation and hypercapnia by allowing the respiratory rate to increase to 35 breaths per minute and by the administration of sodium bicarbonate. Conceivably, respiratory acidosis could have had deleterious effects in the groups treated with low tidal volumes in the other two studies. Finally, the other studies had many fewer patients, thus reducing the statistical power to find a treatment effect.

There has also been considerable interest in the optimal level of positive end-expiratory pressure in patients with acute lung injury and the acute respi-

TABLE 3. HISTORY OF ALTERNATIVE VENTILATORY STRATEGIES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME.

VENTILATORY STRATEGY	YEAR	TYPE OF STUDY	NO. OF PATIENTS	FINDINGS	STUDY
High levels of positive end-expiratory pressure	1975	Observational	28	High incidence of pneumothorax	Kirby et al.[76]
Extracorporeal membrane oxygenation	1979	Phase 3 multicenter trial	90	No benefit	Zapol et al.[78]
High-frequency jet ventilation	1983	Phase 3 single-center trial	309	No benefit	Carlon et al.[79]
Prophylactic positive end-expiratory pressure (3 cm of water)	1984	Phase 3 single-center trial	92	No benefit in patients at risk for the acute respiratory distress syndrome	Pepe et al.[80]
Pressure-controlled inverse-ratio ventilation	1994	Observational	9	Inconclusive, needs further study	Lessard et al.[87]
Extracorporeal removal of carbon dioxide	1994	Phase 3 single-center trial	40	No benefit	Morris et al.[93]
Liquid ventilation	1996	Observational	10	Probably safe, needs further study	Hirschl et al.[88]
High-frequency oscillatory ventilation	1997	Observational	17	Probably safe, needs further study	Fort et al.[100]
Prone positioning during ventilation	1997	Observational	13	Inconclusive, needs further study	Mure et al.[82]
Prone positioning during ventilation	2000	Observational	39	Inconclusive, needs further study	Nakos et al.[83]
"Open-lung" approach	1998	Phase 3 single-center trial	53	Decreased 28-day mortality (no data on hospital mortality [as compared with conventional ventilation])	Amato et al.[10d]
Low tidal volumes	1998	Phase 3	120	No benefit in patients at risk for the acute respiratory distress syndrome	Stewart et al.[10e]
Low tidal volumes	1998	Phase 3	116	No benefit	Brochard et al.[10f]
Low tidal volumes	2000	Phase 3	861	Decreased mortality by 22 percent (as compared with traditional tidal volumes)	Acute Respiratory Distress Syndrome Network[10a]

ratory distress syndrome. It was noted early on that the use of positive end-expiratory pressure could improve oxygenation in these patients, allowing the fraction of inspired oxygen to be reduced.[3,103] The best-documented effect of positive end-expiratory pressure on lung function is an increase in functional residual capacity,[107] probably as a result of the recruitment of collapsed alveoli.[108] Although lung injury was prevented in rats by the prophylactic use of positive end-expiratory pressure,[64] the prophylactic use of a positive end-expiratory pressure of 8 cm of water in patients at risk for the acute respiratory distress syndrome was not successful.[96]

Recently, Amato et al. used an "open-lung" approach to mechanical ventilation in patients with acute lung injury and the acute respiratory distress syndrome.[40] In addition to a low tidal volume and pressure-controlled inverse-ratio ventilation, the protocol included raising the level of positive end-expiratory pressure above the lower inflection point on a pressure–volume curve for each patient in an attempt to ensure adequate recruitment of atelectatic lung. With this approach, mortality was reduced. However, the adoption of this approach cannot yet be recommended for several reasons. First, this study was small, involving only 53 patients and only a single center. Second, mortality in the group treated with conventional ventilation was unusually high (71 percent), suggesting that the high tidal volume used may have been especially injurious. Furthermore, the difference in mortality between the two groups was only apparent at 28 days; the rates of survival until hospital discharge were not significantly different between the two groups. Third, a reliable measurement of the lower inflection point of the pressure–volume curve is technically difficult and usually requires sedation and paralysis of the patient.

In spite of these issues, the study by Amato et al. raises the possibility that improved alveolar recruitment with the use of higher levels of positive end-expiratory pressure than were used in the NIH study[10c] might further reduce ventilator-associated lung injury. This possibility is currently being tested in a new NIH Acute Respiratory Distress Syndrome Network ventilation trial. A number of alternative approaches to conventional mechanical ventilation have also been proposed, including prone positioning of the patient during ventilation,[6,9,87,99-102] but have not yet been proved to be beneficial (Table 3).

Fluid and Hemodynamic Management

The rationale for restricting fluids in patients with acute lung injury and the acute respiratory distress syndrome is to decrease pulmonary edema. Studies in animals with acute lung injury indicated that the degree of edema was reduced if left atrial pressure was lowered.[23,109] Some clinical studies have supported this hypothesis.[110-112] Soon, a randomized trial of fluid management designed to compare restricted with liberal fluid management based on monitoring hemodynamics with either a pulmonary-artery catheter or a central venous catheter will be carried out by the NIH Acute Respiratory Distress Syndrome Network. While we await these results, a reasonable objective is to maintain the intravascular volume at the lowest level that is consistent with adequate systemic perfusion, as assessed by metabolic acid–base balance and renal function. If systemic perfusion cannot be maintained after the restoration of intravascular volume, as is the case in patients with septic shock, treatment with vasopressors is indicated to restore end-organ perfusion and normalize oxygen delivery.[23] However, on the basis of the negative results of clinical trials, the use of supranormal levels of oxygen delivery cannot be recommended.[113,114]

Surfactant Therapy

Because of the success of surfactant-replacement therapy in infants with the neonatal respiratory distress syndrome,[115] surfactant replacement has been proposed as a treatment for patients with acute lung injury and the acute respiratory distress syndrome. However, in one study, treatment with a synthetic surfactant had no effect on oxygenation, the duration of mechanical ventilation, or survival.[116] There are several possible explanations for the negative results. First, the surfactant was delivered as an aerosol, and less than 5 percent may have reached the distal air spaces.[117] Also, the product used, a protein-free phospholipid preparation, may not be the most effective for patients with acute lung injury and the acute respiratory distress syndrome. Newer preparations of surfactant that contain recombinant surfactant proteins and new approaches to their instillation, including tracheal instillation and bronchoalveolar lavage, are being evaluated in clinical trials.

Inhaled Nitric Oxide and Other Vasodilators

Nitric oxide is a potent vasodilator that can be delivered to the pulmonary vasculature by inhalation without causing systemic vasodilation. Although observational studies suggested that inhaled nitric oxide might be beneficial in patients with acute lung injury and the acute respiratory distress syndrome,[118] the results of randomized, double-blind studies have been discouraging. In a phase 2 study, inhaled nitric oxide did not reduce mortality or reduce the duration of mechanical ventilation.[119] The improvements in oxygenation with this treatment were small and were not sustained, and pulmonary-artery pressure decreased very little, and only on the first day of treatment. Also, a recent phase 3 study of inhaled nitric oxide showed that it had no effect on either mortality or the duration of mechanical ventilation.[120] Thus, inhaled nitric oxide cannot be recommended for the routine treatment of acute lung injury and the acute

respiratory distress syndrome, but it may be useful as a rescue therapy in patients with refractory hypoxemia. Treatment with several less selective vasodilators, including sodium nitroprusside,[121] hydralazine,[121] alprostadil (prostaglandin E_1),[123,124] and epoprostenol (prostacyclin),[125] has also not been shown to be beneficial.

Glucocorticoids and Other Antiinflammatory Agents

Recognition of the inflammatory nature of the lung injury in acute lung injury and the acute respiratory distress syndrome prompted interest in antiinflammatory treatments, particularly glucocorticoids. However, glucocorticoids had no benefit when they were given before the onset of the disease or early in its course.[126-128] More recently, glucocorticoids have been used to treat the later, fibrosing-alveolitis phase of the disease. Encouraging results were reported in preliminary studies[129,130] and in a small randomized trial of 24 patients.[131] A larger randomized, multicenter U.S. trial of treatment with high-dose methylprednisolone for at least seven days is under way. Because treatment with high-dose methylprednisolone may increase the incidence of infection, the routine use of this drug in patients with established acute lung injury and the acute respiratory distress syndrome cannot be recommended until results of a large multicenter trial become available.

A short course of high-dose glucocorticoids could be considered as rescue therapy in patients with severe disease that is not resolving. In addition to glucocorticoids, other antiinflammatory agents designed to interrupt the process of acute lung injury have been investigated but have proved unsuccessful (Table 4). The failure may reflect the complexity and redundancy of the inflammation in acute lung injury[12,18,19] or the inability to deliver these agents early enough in the course of the illness.

Acceleration of Resolution

Recognition of the importance of the resolution phase of acute lung injury and the acute respiratory distress syndrome has stimulated interest in strategies to hasten patients' recovery from lung injury. Experimentally, removal of pulmonary edema fluid from the alveolar space can be enhanced by both catecholamine-dependent and catecholamine-independent mechanisms, including those increased by inhaled and systemic beta-agonists.[79-81,133-135] Beta-agonists are appealing candidates because they are already in wide clinical use and have no serious side effects, even in critically ill patients.[136] Treatment with beta-agonists may also increase the secretion of surfactant and perhaps exert an antiinflammatory effect, thus helping to restore vascular permeability of the lung.[137,138]

Since acute injury to epithelial type I cells causes denudation of the alveolar epithelium,[22,130] an additional approach to hastening the resolution of acute lung injury and the acute respiratory distress syndrome is to accelerate reepithelialization of the alve-

TABLE 4. RESULTS OF CLINICAL TRIALS OF PHARMACOLOGIC TREATMENT FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME.

TREATMENT	YEAR	TYPE OF STUDY	NO. OF PATIENTS	FINDINGS	STUDY
Glucocorticoids (during the acute phase)	1987	Phase 3	87	No benefit	Bernard et al.[126]
Glucocorticoids (during the acute phase)	1988	Phase 3	59	No benefit	Luce et al.[127]
Alprostadil					
Intravenous	1989	Phase 3	100	No benefit	Bone et al.[124]
Liposomal	1999	Phase 3	350	Stopped for lack of efficacy	Abraham et al.[128]
Surfactant	1996	Phase 3	725	No benefit; new preparations and methods of delivery now being studied	Anzueto et al.[141]
Glucocorticoids during the fibrosing alveolitis phase	1998	Phase 3	24	Decreased mortality, but study was small	Meduri et al.[131]
Inhaled nitric oxide	1998	Phase 2	177	No benefit	Dellinger et al.[139]
Inhaled nitric oxide	1999	Phase 3	203	No benefit	Payen et al.[140]
Ketoconazole	2000	Phase 2	234	No benefit	NIH Acute Respiratory Distress Syndrome Network[142]
Pentoxifylline	1998	Phase 3	214	Stopped for lack of efficacy	Bernard G: unpublished data
Lisofylline	1999	Phase 2–3	235	Stopped for lack of efficacy	Unpublished data

*NIH denotes National Institutes of Health.

olar barrier (Fig. 4). The proliferation of alveolar epithelial type II cells is controlled by a number of epithelial growth factors, including keratinocyte growth factor. Experimentally, administration of keratinocyte growth factor protects against lung injury,[140,141] probably in part by increasing the proliferation of alveolar type II cells and the clearance rate of alveolar fluid[142] and by inducing antioxidant effects,[143] and perhaps by reducing lung endothelial injury.[144-146] These findings raise the possibility that an epithelium-specific growth factor could be used to accelerate the resolution of the syndrome. Overall, strategies directed at restoring the function of alveolar epithelium deserve careful evaluation.[146]

CONCLUSIONS

In conclusion, substantial progress has been made in the understanding of acute lung injury and the acute respiratory distress syndrome. More information regarding epidemiology and pathogenesis has become available, and the importance of the resolution phase of the illness has been recognized, opening up new avenues for therapeutic intervention. Although progress in specific treatments has lagged behind basic research, the formation of the NIH Acute Respiratory Distress Syndrome Network led to a clinical trial of a ventilation strategy involving low tidal volumes, which reduced mortality by 22 percent.[106] Large, prospective, randomized trials of new ventilatory and pharmacologic strategies may further reduce mortality from this common clinical syndrome.

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Mechanical Ventilation in ARDS*

A State-of-the-Art Review

Timothy D. Girard, MD; and Gordon R. Bernard, MD, FCCP

Mechanical ventilation is an essential component of the care of patients with ARDS, and a large number of randomized controlled clinical trials have now been conducted evaluating the efficacy and safety of various methods of mechanical ventilation for the treatment of ARDS. Low tidal volume ventilation (≤ 6 mL/kg predicted body weight) should be utilized in all patients with ARDS as it is the only method of mechanical ventilation that, to date, has been shown to improve survival. High positive end-expiratory pressure, alveolar recruitment maneuvers, and prone positioning may each be useful as rescue therapy in a patient with severe hypoxemia, but these methods of ventilation do not improve survival for the wide population of patients with ARDS. Although not specific to the treatment of ARDS, protocol-driven weaning that utilizes a daily spontaneous breathing trial and ventilation in the semirecumbent position have proven benefits and should be used in the management of ARDS patients. *(CHEST 2007; 131:921–929)*

Key words: acute lung injury; ARDS; mechanical ventilation; positive end-expiratory pressure; prone position; tidal volumes

Abbreviations: ALI = acute lung injury; ALVEOLI = Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure To Obviate Lung Injury; APACHE = acute physiology and chronic health evaluation; APRV = airway pressure release ventilation; ARMA = Respiratory Management in Acute Lung Injury/Acute Respiratory Distress Syndrome; CI = confidence interval; FIO_2 = fraction of inspired oxygen; IL = interleukin; IRV = inverse ratio ventilation; PEEP = positive end-expiratory pressure; Pflex = lower inflection point on the pressure-volume curve of the respiratory system

Prior to the development and widespread use of positive-pressure ventilators, acute lung injury (ALI) and ARDS, often termed *double pneumonia*, were nearly universally fatal forms of respiratory failure. However, in 1967 when Ashbaugh and colleagues[1] described the clinical entity that they called "acute respiratory distress in adults," positive-pressure mechanical ventilation was an important component of the care of patients with acute respiratory failure, and it was clear that this therapy was vital to the survival of patients with ARDS. Over the next 3 decades, general improvements in critical care contributed to some decline in the mortality associated with ARDS, but these benefits reached a plateau by the 1990s.[2]

Later that decade, the first randomized trials were conducted showing that an experimental method of mechanical ventilation (low tidal volume ventilation) could reduce mortality compared with traditional methods of ventilation. This article will review these and other clinical trials and make recommendations regarding the use of mechanical ventilation in the treatment of ARDS patients.

Low Tidal Volume Ventilation

Early interest in low tidal volume ventilation was prompted by animal studies[3,4] showing that ventilation with large tidal volumes and high inspiratory

From the Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN.

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Correspondence to: Timothy D. Girard, MD, 6th Floor MCE, Suite 6300, Center for Health Services Research, Vanderbilt University School of Medicine, Nashville, TN 37232-8300; e-mail: timothy.girard@vanderbilt.edu

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pressures resulted in the development of ALI characterized by hyaline membranes and inflammatory infiltrates. While tidal volumes of 10 to 15 mL/kg had traditionally been used in the majority of patients with respiratory failure,[5] it was recognized in the mid-1960s that ARDS resulted in a significant reduction in the amount of normally aerated lung tissue. The "baby lung" that is typical of ARDS patients was markedly overdistended by high tidal volumes.[6]

Multiple animal studies of excessive alveolar distension, such as that seen in ARDS, provided investigators with a scientific rationale to hypothesize that low tidal volume ventilation would improve mortality among patients with ARDS. High tidal volume ventilation incites an inflammatory response in the lung that promotes systemic inflammation, often resulting in multiple organ system dysfunction. Tremblay et al[7] observed that high tidal volume ventilation in rats resulted in increased levels of inflammatory mediators (ie, tumor necrosis factor-α, interleukin [IL]-6, and IL-10) in BAL fluid, and von Bethmann et al[8] confirmed that increased levels of tumor necrosis factor-α and IL-6 are released into the circulation from lungs ventilated with high tidal volumes. Kolobow et al[3] evaluated sheep that had been subjected to high or low tidal volume ventilation and found that those ventilated with high tidal volumes died with severe respiratory failure and shock within 48 h. These studies prompted Hickling and colleagues[9] to use a low tidal volume/low inspiratory pressure strategy of ventilation in patients with severe ARDS, and a retrospective analysis of a series of 80 such patients indicated that mortality was significantly lower than that predicted by acute physiology and chronic health evaluation (APACHE) II scores (16% vs 39.6%, respectively; $p < 0.001$).

In the late 1990s, four randomized controlled trials[10–13] were conducted to evaluate the benefit of low tidal volume ventilation in ARDS patients compared with traditional tidal volume ventilation (Table 1). Only one of these trials, conducted by Amato and colleagues,[10] showed a significant reduction in mortality in the experimental treatment group. Patients randomized to tidal volumes of ≤ 6 mL/kg actual body weight and driving pressures of < 20 cm H_2O were significantly less likely to die during the 28-day study period than were patients randomized to the traditional 12 mL/kg actual body weight tidal volumes and unlimited driving pressures (38% vs 71%, respectively; $p = 0.001$). A similar mortality benefit was not shown in the three other randomized trials,[11–13] and the high mortality in the control group studied by Amato et al[10] made the results of this trial subject to criticism. All four studies had limited statistical power due to small sample sizes, and the differences in tidal volume between treatment groups achieved in the three negative trials were notably smaller than that in the one positive trial, as follows: tidal volumes were 7.0 vs 10.7 mL/kg ideal body weight in the trial by Stewart et al[11]; 7.1 vs 10.3 mL/kg dry body weight in the trial by Brochard et al[12]; and 7.3 vs 10.2 mL/kg predicted body weight in the trial by Brower et al.[13]

In light of the limitations and conflicting results of the aforementioned randomized trials, a large, well-conducted trial was needed to definitively determine

Table 1—*Randomized Controlled Trials Evaluating Strategies of Mechanical Ventilation for the Treatment of ARDS

Study	Patients, No.	Intervention	Mortality Rates†	p Value
Amato et al[10]	53	≤ 6 mL/kg ABW, V_T < 20 cm H_2O Pdriving	38% vs 71%‡	0.001
Stewart et al[11]	120	≤ 6mL/kg IBW, V_T ≤ 30 cm H_2O Pplat	50% vs 47%	0.72
Brochard et al[12]	116	6–10 mL/kg IBW, V_T, 28–30 cm H_2O Pplat	47% vs 38%§	0.38
Brower et al[13]	92	≤ 8 mL/kg PBW, V_T ≤ 30 cm H_2O Pplat	50% vs 46%	0.61
ARMA[14]	861	≤ 6mL/kg PBW, V_T ≤ 30 cm H_2O Pplat	31% vs 40%	0.007
Derdak et al[24]	148	HFOV	37% vs 52%‖	0.10
Bollen et al[22]	61	HFOV	45% vs 32%‖	0.39
ALVEOLI[20]	549	High-PEEP protocol	28% vs 26%	0.48
Villar et al[21]	103	5–8 mL/kg PBW, V_T, PEEP of Pflat + 2 cm H_2O	34% vs 56%	0.04
Cattinoni et al[25]	304	Prone position 6 h/d for 10 d	63% vs 59%¶	0.68
Guerin et al[26]	791	Prone position 8 h/d	32% vs 32%†	0.77
Mancebo et al[27]	136	Prone position 20 h/d	30% vs 52%	0.22

*ABW = actual body weight; V_T = tidal volume; Pdriving = driving pressure; IBW = ideal body weight; Pplat = plateau pressure; PBW = predicted body weight; HFOV = high-frequency oscillatory ventilation.

†Values are given as the in-hospital mortality rates of intervention vs control group, unless otherwise noted.

‡28-day mortality rate.

§60-day mortality rate.

‖30-day mortality rate.

¶180-day mortality rate.

the effect of low tidal volume ventilation in ARDS patients. In response to this need, from 1996 to 1999 the National Heart, Lung, and Blood Institute (NHLBI) ARDS Network enrolled 861 patients at 10 institutions in a randomized controlled trial known as the Respiratory Management in Acute Lung Injury/ARDS (ARMA) trial (originally a factorial trial known as KARMA, the Ketoconazole and Respiratory Management in Acute lung injury/ARDS). ARMA[14] compared a ventilatory protocol using tidal volumes of ≤ 6 mL/kg predicted body weight and maintaining plateau pressures of ≤ 30 cm H_2O with conventional mechanical ventilation using higher tidal volumes. The lower tidal volume protocol in ARMA achieved more pronounced differences between the intervention and control groups in tidal volume (6.2 vs 11.8 mL/kg predicted body weight, respectively) and plateau pressure (25 vs 33 cm H_2O, respectively) than those achieved in previous studies. The hospital mortality rate was significantly reduced in the low tidal volume group compared with the control group (31% vs 39.8%, respectively; $p = 0.007$) [Fig 1]. Additionally, patients treated with low tidal volume ventilation had a greater mean (± SD) number of days free of mechanical ventilation (12 ± 11 vs 10 ± 11 days, respectively; $p = 0.007$) and a greater number of days free of nonpulmonary organ failure (15 ± 11 vs 12 ± 11 days, respectively; $p = 0.006$).[14]

Compared with the previous studies of low tidal volume ventilation, ARMA had considerable power to detect a difference in clinical outcomes due to the large number of patients enrolled (Table 1). And, as described above, the difference in tidal volumes used in the two study groups in ARMA was larger than that obtained in other studies.[13] In fact, it has been proposed that the mortality benefit demonstrated in ARMA was attributable to a high mortality rate in the control group resulting from tidal volumes that were higher than the standard of care. However, in an international survey of physicians' practices in 1992,[15] a broad range of tidal volumes used in ARDS patients was reported, indicating that no uniform standard of care existed, and more than half of the respondents reported using tidal volumes that were as high as or higher than those used in the ARMA control group.

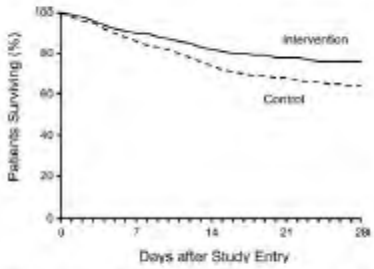

FIGURE 1. Kaplan-Meier analysis of survival during the first 28 days after randomization in patients with ALI and ARDS. The in-hospital mortality rate was 31.0% in the group treated with lower tidal volumes compared with 39.8% in the group treated with traditional tidal volumes ($p = 0.007$; 95% CI for the difference between groups, 2.4 to 15.3%). A Kaplan-Meier analysis of survival during the first 180 days after study entry is presented in the publication by the Acute Respiratory Distress Syndrome Network.[14]

The only method of mechanical ventilation that has been shown in randomized controlled trials to improve survival in patients with ARDS is low tidal volume ventilation (Table 1, Fig 2). In ARMA, ventilation with low tidal volumes and plateau pressures resulted in a nearly 9% absolute reduction in the risk of death.[14] Therefore, high tidal volumes and high plateau pressures should be avoided in patients with ARDS, and critical care clinicians should utilize low tidal volumes as part of a ventilatory protocol that also limits plateau pressure. Specifically, it is recommended that practitioners utilize the ventilatory protocol outlined by the ARDS Network investigators in an ARMA publication from 2000,[14] as this protocol involved more than the use of low tidal volumes, as follows: tidal volume size should be based on predicted body weight (calculated from sex and height) rather than actual body weight; tidal volumes should be systematically adjusted (from 4 to 6 mL/kg predicted body weight) to maintain a plateau pressure of ≤ 30 cm H_2O; the respiratory rate should be titrated as needed (from 6 to 35 breaths/min) to maintain a pH of 7.3 to 7.45; and an appropriate combination of fraction of inspired oxygen (FIO_2) and positive end-expiratory pressure (PEEP) should be used to achieve adequate oxygenation (PaO_2, 55 to 80 mm Hg, or pulse oximetric saturation, 88 to 95%).

Since the publication of ARMA, low tidal volume ventilation has remained underutilized in the treatment of patients with ARDS.[16–18] Common barriers to the initiation of low tidal volume ventilation include unwillingness to relinquish control of the ventilator, failure to recognize patients as having ALI/ARDS, and perceived contraindications to low tidal volume ventilation.[19] Significant barriers to the continuation of low tidal volume ventilation include concerns regarding patient discomfort and tachypnea or hypercapnia and acidosis.[19]

While barriers to the initiation of low tidal volume ventilation remain a significant challenge, more re-

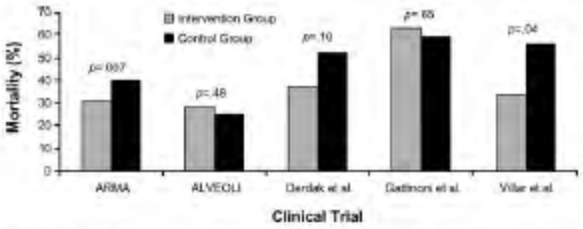

FIGURE 2. Mortality according to treatment group in representative randomized controlled trials evaluating strategies of mechanical ventilation in patients with ALI/ARDS. ARMA compared lower tidal volume ventilation with higher tidal volume ventilation and measured the in-hospital mortality rate.[14] ALVEOLI compared a high-PEEP protocol with lower PEEP and measured the in-hospital mortality rate.[20] Derdak et al[22] compared high-frequency oscillatory ventilation with conventional ventilation and measured the 30-day mortality rate. Gattinoni et al[23] compared prone positioning with conventional ventilation and measured the 180-day mortality rate. Villar et al[24] compared a protocol of lower tidal volumes with PEEP above the P_{flex} with higher tidal volumes and lower PEEP, and measured the in-hospital mortality rate.

cent studies have addressed concerns regarding both hypercapnia and patient discomfort. While an acutely elevated $PaCO_2$ may result in physiologic abnormalities such as vasodilation, tachycardia, and hypotension, multiple studies[20–22] have demonstrated that modest, permissive hypercapnia occurring as a result of lowering tidal volumes and minute ventilation is safe. While permissive hypercapnia is tolerated in the majority of ARDS patients, those with preexisting metabolic acidosis may require treatment to prevent worsening acidosis. In fact, ARMA[14] allowed the use of both increased respiratory rates (up to 35 breaths/min) and bicarbonate infusions in such patients.

No evidence exists supporting the notion that low tidal volume ventilation results in additional patient discomfort or the need for increased sedation compared with ventilation using larger tidal volumes. In fact, in ARMA the percentage of days during which sedation was used among patients ventilated with low tidal volumes was no different than that among patients ventilated with traditional tidal volumes (*ie*, 68% ± 26% vs 68% ± 24% in patients discharged home and breathing without assistance; 73% ± 24% vs 71% ± 26% in patients who died).[14] Additionally, a recent secondary analysis[23] of patients who were enrolled at one center during ARMA demonstrated that low tidal volume ventilation was associated neither with increased dose nor with increased duration of sedatives in patients with ARDS. Therefore, patients with ARDS who are being ventilated with low tidal volumes should be managed with the sedation strategies recommended for all critically ill, mechanically ventilated patients. Specifically, sedation protocols using standardized sedation scales[24,25] and sedation goals[26] have been proven to reduce the duration of mechanical ventilation, and preference should be given to the daily interruption of sedation[27] and the use of intermittent boluses rather than continuous infusions,[28] when tolerated.

Some have proposed that high-frequency oscillatory ventilation is an ideal mode of ventilation for ARDS patients as it is the natural culmination of low tidal volume ventilation. This mode of ventilation rapidly delivers small tidal volumes that are typically 1 to 5 mL/kg.[29] Animal studies[30] as well as observational human studies[31] have suggested that high-frequency oscillatory ventilation improves gas exchange and reduces ventilator-induced lung injury. However, both randomized controlled trials[32,33] that have been conducted to date to evaluate the efficacy of high-frequency oscillatory ventilation in the treatment of ARDS have failed to demonstrate an improvement in mortality (Table 1). The larger of the two trials, conducted by Derdak and colleagues,[22] enrolled 148 ARDS patients and noted that patients who were randomized to high-frequency oscillatory ventilation experienced an early improvement in oxygenation that was not seen in patients who were randomized to conventional ventilation ($p = 0.0008$). The 30-day mortality rate was lower in the high-frequency oscillatory ventilation group compared with that in the control group, but this difference was not statistically significant (37% vs 52%, respectively; $p = 0.10$). Additionally, subjects in the control group were ventilated with higher tidal volumes (mean tidal volume at 72 h, 8 ± 2 mL/kg actual body weight). Therefore, an adequately

powered randomized trial is needed to determine the efficacy of high-frequency oscillatory ventilation compared with low tidal volume ventilation before its use can be widely recommended.

High PEEP and Alveolar Recruitment

PEEP is an essential component of mechanical ventilation for patients with ARDS that should be utilized to increase the proportion of nonaerated lung, resulting in improved oxygenation. Traditionally, PEEP values of 5 to 12 cm H_2O have been used in the ventilation of patients with ARDS.[34] However, it currently remains unclear whether these values are ideal since randomized trials[34,35,36] have not shown that higher levels of PEEP lead to a reduction in mortality rate.

Early observations that PEEP greatly improves oxygenation in patients with ARDS led to its widespread use in such patients, but the level of PEEP needed to achieve maximum benefit with minimum complications was never established. Additionally, animal models[37] have suggested that repetitive opening and closing of the alveoli during the respiratory cycle can promote lung injury. Therefore, several randomized trials evaluated the efficacy of high levels of PEEP in the treatment of ARDS. In the study of a protective-ventilation strategy, by Amato and colleagues,[10] PEEP was significantly higher in the intervention group compared with the control group (mean PEEP on days 2 to 7, 13.2 ± 0.4 vs 9.3 ± 0.8 cm H_2O; $p < 0.01$). Villar et al[38] evaluated a similar strategy in a randomized controlled trial that enrolled patients with persistent ARDS (the PaO_2/FiO_2 ratio remained ≤ 200 for at least 24 h while standard ventilator settings were used). Patients in the intervention group were ventilated with tidal volumes of 5 to 8 mL/kg predicted body weight, and PEEP was set on day 1 at 2 cm H_2O above P_{flex}, defined as the lower inflection point on the pressure-volume curve of the respiratory system. The control group was ventilated with tidal volumes of 9 to 11 mL/kg predicted body weight and a PEEP of ≥ 5 cm H_2O. This difference resulted in a significantly higher PEEP among intervention patients compared with control patients (mean PEEP on day 1, 14.1 ± 2.8 vs 9.0 ± 2.7 cm H_2O, respectively; $p < 0.001$) as well as a significantly lower ICU mortality rate among intervention patients (32% vs 53.3%, respectively; $p = 0.04$). Ranieri et al[35] determined that a similar ventilatory strategy (mean PEEP at 2 to 3 h, 14.8 ± 2.7 vs 6.5 ± 1.7 cm H_2O, respectively; mean tidal volume at 2 to 3 h, 7.6 ± 1.1 vs 11.1 ± 1.9 mL/kg, respectively) resulted in an attenuation of the cytokine response observed in patients who were ventilated with higher tidal volumes and lower PEEP. But neither these findings nor the significantly lower mortality rates observed in the intervention groups in the trials of both Villar et al[38] and Amato et al[10] could be solely attributed to higher levels of PEEP since the intervention strategies in these trials employed both low tidal volumes and high levels of PEEP. The isolated benefit to survival of low tidal volume ventilation was demonstrated in ARMA,[14] as discussed previously, since patients in the intervention group were treated with levels of PEEP that were no different than those utilized in the control group. But another trial was needed to evaluate the efficacy of high PEEP in which all patients received low tidal volume ventilation.

In order to determine the isolated benefit of high levels of PEEP in patients with ARDS, the National Heart, Lung, and Blood Institute ARDS Network conducted another large randomized controlled trial known as the ALVEOLI trial (Assessment of Low tidal Volume and Elevated End-Expiratory Pressure To Obviate Lung Injury).[39] Patients were randomized to a ventilatory protocol utilizing high levels of PEEP (12 to 24 cm H_2O) or low levels of PEEP (5 to 24 cm H_2O); all patients were ventilated with low tidal volumes (6 mL/kg predicted body weight). PEEP was significantly higher among intervention patients compared with control patients throughout the study period (mean PEEP on day 1, 14.7 ± 3.5 vs 8.9 ± 3.5 cm H_2O, respectively; mean PEEP on day 3, 12.9 ± 4.5 vs 8.5 ± 3.7 cm H_2O, respectively; mean PEEP on day 7, 12.9 ± 4.0 vs 8.4 ± 4.3 cm H_2O, respectively). Although the patients treated with higher PEEP clearly experienced increases in oxygenation, as measured by the PaO_2/FiO_2 ratio, compared with patients treated with lower PEEP, the in-hospital mortality rate was similar in the two treatment groups ($p = 0.48$) [Table 1]. The duration of mechanical ventilation and the duration of nonpulmonary organ failure were similar in the two groups as well.

The ALVEOLI trial also evaluated the safety and efficacy of recruitment maneuvers in the first 50 patients randomized to the high-PEEP group. These maneuvers, like high levels of PEEP, are intended to promote alveolar recruitment and to attenuate the injurious effects of the repetitive opening and closing of the alveoli. Continuous positive airway pressure of 35 to 40 cm H_2O was applied for 30 s, and the results were compared to those of a sham recruitment maneuver. Because the interventions resulted in only small and transient increases in oxygenation, they were discontinued. Such maneuvers have been associated with transient but significant hypotension and hypoxemia,[39] and their long-term benefit re-

mains unproven; therefore, their routine use is not recommended in patients with ARDS.

Prone Positioning

Mechanical ventilation in the prone position was first proposed in 1974 by Bryan,[40] who suggested that the procedure would result in better expansion of the dorsal lung regions, thus improving oxygenation. Shortly thereafter, two nonrandomized studies[41,42] reported the successful use of prone positioning as an adjunct to mechanical ventilation for the treatment of ARDS, with patients experiencing improved oxygenation. In the 3 decades following these initial reports, interest in prone positioning has remained strong, although the physiologic mechanisms leading to improved oxygenaiton during prone positioning are not yet fully understood.[43] The existing evidence suggests that mechanical ventilation in the prone position improves oxygenation and respiratory mechanics via multiple mechanisms, including alveolar recruitment,[44] redistribution of ventilation toward dorsal areas resulting in improved ventilation/perfusion matching,[45,46] and the elimination of compression of the lungs by the heart.[47] Additionally, prone ventilation may lower the incidence of ventilator-induced lung injury by reducing parenchymal lung stress and lung strain.[48]

Three randomized controlled trials[49–51] of prone positioning during mechanical ventilation in ARDS patients have shown consistent findings. While the majority of patients experience improved oxygenation in response to prone positioning, this method of mechanical ventilation does not lead to a reduction in mortality (Table 1).[49–51] In the largest of these trials, Guerin and colleagues[50] enrolled 791 patients with acute respiratory failure (413 had ALI/ARDS), randomizing each to prone position placement for at least 8 h daily or to standard therapy in the supine position. PaO_2/FIO_2 ratio was significantly higher throughout the 28-day study period in the prone position group ($p < 0.001$), but this physiologic change did not decrease the mortality rate at 28 days (prone position, 32.4%; supine position, 31.5%; $p = 0.77$) or at 90 days (prone position, 43.3%; supine position, 42.2%; $p = 0.74$). Prone positioning did result in a significantly higher incidence of several complications compared with ventilation in the supine position, including selective intubation ($p = 0.01$), endotracheal tube obstruction ($p = 0.002$), and pressure sores ($p = 0.008$). Gattinoni et al[49] enrolled ALI/ARDS patients exclusively and reported similar findings. A *post hoc* analysis of patients with the lowest PaO_2/FIO_2 ratio (≤ 88) found that the 10-day mortality rate was significantly lower in the prone position group compared with the supine position group (23.1% vs 47.2%, respectively; relative risk, 0.49; 95% confidence interval [CI], 0.25 to 0.95). Prone positioning was similarly beneficial for patients with high severity-of-illness scores or high tidal volumes, but the benefits noted in the *post hoc* analyses did not persist beyond ICU discharge.

Despite consistently leading to short-term improvements in oxygenation, prone positioning during mechanical ventilation has failed to improve mortality rates in multiple randomized controlled trials (Table 1) and cannot be recommended for the broad population of patients requiring mechanical ventilation due to ARDS. However, for those patients requiring potentially injurious levels of FIO_2 (*ie*, $> 60\%$) or plateau pressure (ie, > 30 cm H_2O) due to persistent, severe hypoxemia, whose conditions are being managed in an experienced institution, prone positioning may be considered as a short-term rescue therapy. In such circumstances, the potential for life-threatening complications of prone positioning, including accidental dislodgment of the endotracheal tube or central venous catheters and endotracheal tube obstruction, should be weighed against the short-term benefit of improved oxygenation.

Alternative Modes/Methods of Mechanical Ventilation

Both large trials conducted by the ARDS Network utilized the volume assist/control mode of ventilation. In fact, this was the only mode of ventilation used in each of the three randomized controlled trials of ARDS in which the intervention significantly reduced mortality.[10,14,25] Although the efficacy of low tidal volume ventilation is not necessarily contingent on the use of the volume assist/control mode of ventilation, it continues to be the recommended mode in the general population of patients with ARDS.

However, other modes of mechanical ventilation are available and may provide critical care and respiratory care practitioners with alternative treatments for ARDS patients with refractory hypoxemia. In addition to the previously described high-frequency oscillatory ventilation, inverse ratio ventilation (IRV) and airway pressure release ventilation (APRV) may be considered in difficult-to-manage ARDS patients. IRV, during which the ratio of inspiratory time to expiratory time exceeds 1, can be achieved using either volume or pressure modes of ventilation. Prolongation of the inspiratory time results in increased mean airway pressures, often improving oxygenation. APRV uses high continuous airway pressure to promote alveolar recruitment and

to maintain adequate lung volume, and a time-cycled release phase to a lower pressure to supplementing spontaneous minute ventilation.[58] By allowing unrestricted spontaneous breathing throughout the ventilator cycle, APRV allows for better ventilation of dependent lung regions; spontaneous breathing reduced atelectasis and improved end-expiratory lung volume in oleic acid-induced lung injury.[33] This can lead to improved ventilation-perfusion matching and better oxygenation, changes that have been demonstrated in patients with ARDS who have received ventilation with APRV with spontaneous breathing.[34] While both IRV and APRV may provide short-term physiologic benefits to patients with severe ARDS, their widespread use is not recommended due to the lack of randomized controlled trials demonstrating their efficacy against clinically relevant end points in ARDS, such as mortality and duration of mechanical ventilation.

Partial liquid ventilation using perfluorocarbons for the treatment of ARDS has been evaluated in two randomized controlled trials. Hirschl et al[35] randomized 90 patients with ARDS to perflubron or conventional ventilation and found no difference in mortality or duration of mechanical ventilation, while Kacmarek et al[36] randomized 311 ARDS patients to receive high-dose perflubron, low-dose perflubron, or conventional ventilation and found no improvement in outcome. Therefore, partial liquid ventilation is not recommended for the treatment of ARDS.

Noninvasive positive-pressure ventilation (ie, mechanical ventilation administered without the use of an invasive endotracheal airway) has been used successfully for the treatment of acute respiratory failure in a number of clinical trials, and it has been suggested[37] that noninvasive positive-pressure ventilation may be useful for the treatment of ARDS. However, randomized trials evaluating the efficacy and safety of noninvasive positive-pressure ventilation in patients with hypoxemic respiratory failure have failed to show a benefit in subgroups of patients with ARDS.[38] Therefore, while noninvasive positive-pressure ventilation may have value in some ARDS patients who are carefully selected by experienced practitioners, its routine use in this population of patients is not recommended.[39]

Liberation From Mechanical Ventilation

As the majority of patients who are mechanically ventilated for acute respiratory failure spend approximately two thirds of their time on the ventilator in the "weaning" period,[54] a systematic, evidence-based approach to liberating ARDS patients from mechanical ventilation is an essential component of their care. This approach should be protocol-directed, and a daily spontaneous breathing trial should be the central component of that protocol.

Several randomized controlled trials[60–63] have demonstrated that the duration of mechanical ventilation is significantly reduced in patients who have been assessed once daily with a spontaneous breathing trial, consisting of a period of 30 to 120 min of unassisted breathing. Esteban et al[60] enrolled 546 patients with respiratory failure (319 patients had ALI/ARDS) and randomized those who failed an initial 2-h spontaneous breathing trial to one of four weaning methods. Patients managed with a once-daily spontaneous breathing trial were extubated more quickly than those managed with intermittent mandatory ventilation ($p < 0.006$) and those managed with pressure-support ventilation ($p < 0.04$). Ely et al[61] randomized 300 patients (42 patients had ARDS) to a weaning protocol utilizing a daily spontaneous breathing trial or to usual care and determined that patients managed with the weaning protocol were extubated more quickly than those managed with usual care ($p < 0.001$) [Fig 3]. A T-piece, continuous positive airway pressure, or pressure support ventilation of ≤ 7 cm H_2O may be utilized,[55] and the spontaneous breathing trial should be performed only in patients meeting the following standardized safety criteria: (1) some reversal of the

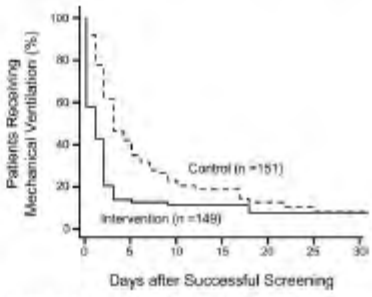

Figure 3. Kaplan-Meier analysis of the duration of mechanical ventilation in medical ICU patients with acute respiratory failure. After adjustment for the severity of illness at baseline (as measured by APACHE II score), age, sex, race, location of the ICU, and duration of intubation before enrollment, a Cox proportional hazards analysis showed that mechanical ventilation was discontinued more rapidly in the intervention group than in the control group (relative risk of successful extubation, 2.13; 95% CI, 1.55 to 2.92; $p < 0.001$). The intervention consisted of a weaning protocol mandating the daily screening of respiratory function followed by 2-h spontaneous breathing trials in those who met the screening criteria. Copyright 1996 Massachusetts Medical Society. All rights reserved.[52]

underlying cause for respiratory failure; (2) PEEP of ≤ 8 cm H_2O and FIO_2 of $\leq 50\%$; (3) hemodynamic stability; and (4) ability to initiate inspiratory efforts.[54] When possible, all mechanically ventilated patients should be placed in a semirecumbent position in order to reduce the incidence of ventilator-associated pneumonia.[55]

Conclusion

In the management of patients with ARDS, low tidal volume ventilation (*ie*, ≤ 6 mL/kg predicted body weight) with the maintenance of plateau pressures of < 30 cm H_2O, when possible, remains the standard of care as it is the only method of mechanical ventilation that has been proven to reduce the mortality rate. While modifications of these parameters could result in even better outcomes than those observed in the ARMA and ALVEOLI trials (Fig 2), randomized controlled trials should be performed to determine the efficacy and safety of such alterations. Other methods, such as high-PEEP ventilation, alveolar recruitment maneuvers, and prone positioning, may be useful as rescue therapy in carefully defined situations of severe hypoxemia, but their use is not widely recommended as these methods do not improve mortality in the broad population of ARDS patients. Ongoing trials are currently evaluating the efficacy of newer modes and methods of mechanical ventilation, such as high-frequency oscillatory ventilation. The results of these studies will guide the management of ARDS patients in the future.

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