Bruno Riou, M.D., Ph.D., Editor

Case Scenario: Pain-associated Respiratory Failure in Chest Trauma

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THE leading cause of death in young people is trauma. Chest trauma has high associated mortality, thus diagnosis and treatment need to be addressed early on presentation.[1] The incidence of rib fractures range from 10% to 26% in traumatic thoracic injury and the number of rib fractures independently predict patients' pulmonary morbidity and mortality.[2] Numerous cardiopulmonary to neurologic causes such as tamponade, hemo- pneumothorax, and cervical spine injury can be implicated (fig. 1). Severe respiratory distress can also result from breathing-dependent pain where parenteral opioids are often insufficient in addressing the pain and associated respiratory failure.[3] Epidural analgesia is associated with reduction in mortality for all patients with multiple rib fractures but is underused, in part due to the potential risks of epidural hematomas.[2,4] Variables that alter the risk of bleeding including age and sex, comorbidities such as diabetes and liver cirrhosis, severity of trauma and degree of resuscitation, and anticoagulation or antiplatelet therapy must also be considered.

We describe a patient under clopidogrel therapy presenting to the intensive care unit (ICU) with severe respiratory distress that improved with epidural analgesia. We provide a discussion of the risks and benefits of neuraxial analgesia in patients presenting with rib-fracture pain-related respiratory failure.

Case Report

A 79-yr-old man with a history of chronic obstructive pulmonary disease, bronchiectasis, coronary artery disease postplacement of bare-metal stent several years ago, hypertension, and diabetes was transferred to our hospital shortly after motor-vehicle collision. Home medications were aspirin 325 mg, clopidogrel 75 mg per day (taken morning of accident), as well as inhaled tiotropium, inhaled fluticasone/salmeterol, albuterol, isosorbide dinitrate, metformin, and simvastatin. On arrival, the patient was hemodynamically stable with pulse oximeter saturations of 94% on a nonrebreather mask with 60% inspired oxygen concentration. Computed tomography imaging revealed second to ninth anterior right rib fractures, fourth through ninth anterior left rib fractures, and posterior 10th and 11th left rib fractures, but without flail chest nor pneumothorax. A small left pleural effusion, left lung and lingular atelectasis, and minimal ground glass opacity in the right upper lobe, and a small right-lower lobe pulmonary contusion were shown (fig. 2). The patient received 3 l lactated Ringer's solution before arriving in our ICU. His Injury Severity Score of 24 was primarily due to rib and lung injuries (16 points), then moderate head and surface injuries (4 points each).

After admission to the surgical ICU, he developed increasing pain-related respiratory distress during the day. Tylenol was administered, and hydromorphone 0.2 mg intravenously produced somnolence, but minimal improvement of respiratory effort and pain. He had an electrocardiogram unremarkable for cardiac ischemia and negative cardiac isoenzymes and brain-natriuertic peptide. Stat upright chest radiograph revealed left lower lobe opacities and bilateral atelectasis, without evidence of pneumothroax or significant injury to the lung parenchyma. He had a weak cough and impaired peak flow of 0.8 l/min (Hudson Respiratory Care Inc., Teleflex Medical, Research Triangle Park, NC). Bilevel positive airway pressure was instituted, but the patient continued to have respiratory and neurologic deterioration.

Intubation with mechanical ventilation or epidural analgesia attempt to improve respiratory function was

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Received from the Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. Submitted for publication February 24, 2012. Accepted for publication November 16, 2012. Support was provided solely from institutional and/or departmental sources. Figures 1-4 were redrawn by Annemarie B. Johnson, C.M.I., Medical Illustrator, Wake Forest University School of Medicine Creative Communications, Wake Forest University Medical Center, Winston-Salem, North Carolina.

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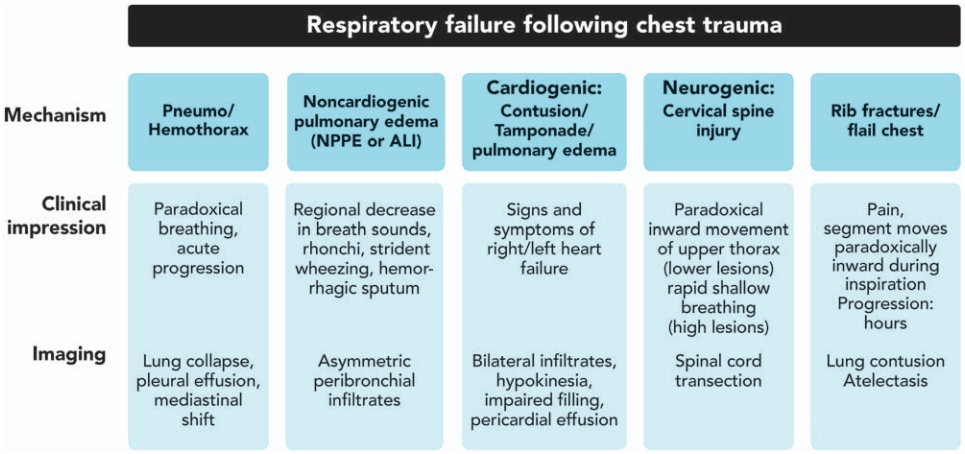


Fig. 1. Mechanism of respiratory failure following trauma. It is essential to completely evaluate the broad differential of respiratory failure following trauma. This includes ruling out non- cardiogenic pulmonary edema, cardiogenic causes, neurologic causes such as cervical spine injury, and pneumothorax and hemothorax. Both the imaging and clinical presentation can share similarities and have distinguishing characteristics.

discussed. Labs, approximately 10 h postadmission revealed a prothrombin time of 12.2 s, an international normalized ratio of 1.1, partial thromboplastin time of 26.3 s, and platelet count of 321,000 μl^{-1}, all within normal limits. Thromboelastogram (TEG®; Haemonetics, Niles, IL) was performed with the following result (reference values in parenthesis): R time: (2-8 min), K (1-3 min), Alpha (55-78 degrees), MA (51-69 mm) (fig. 3). The increased maximum amplitude in the TEG indicated a trend to a hypercoagulable state, thus no platelets or hemostatic interventions were given.[40] Informed consent for epidural placement was obtained, including the bleeding risks associated with trauma and antiplatelet therapy.

A midthoracic epidural catheter was placed uneventfully. Bupivicaine 0.1% and hydromorphone 20 <mu>g /ml epidural mix was bolused at 3 ml and an infusion initiated at 6 ml/h, with improvement in pain control and respiratory function. Peak flow improved to 1.5 l/min and the patient was able to maintain SpO2 100% on 4 l nasal cannula without further use of parenteral opioids. He was discharged to the trauma step-down unit 2 days after epidural placement. Clopidogrel was held until the catheter was removed 5 days after placement.

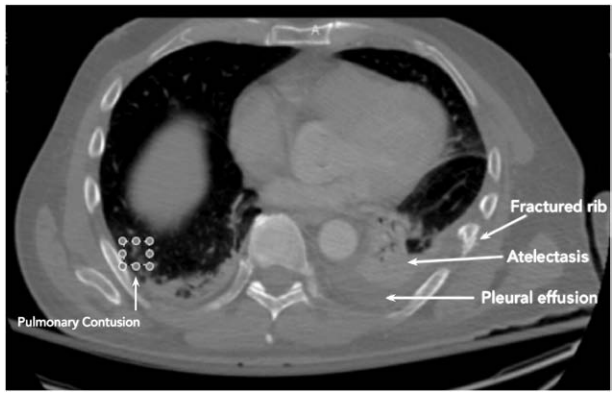


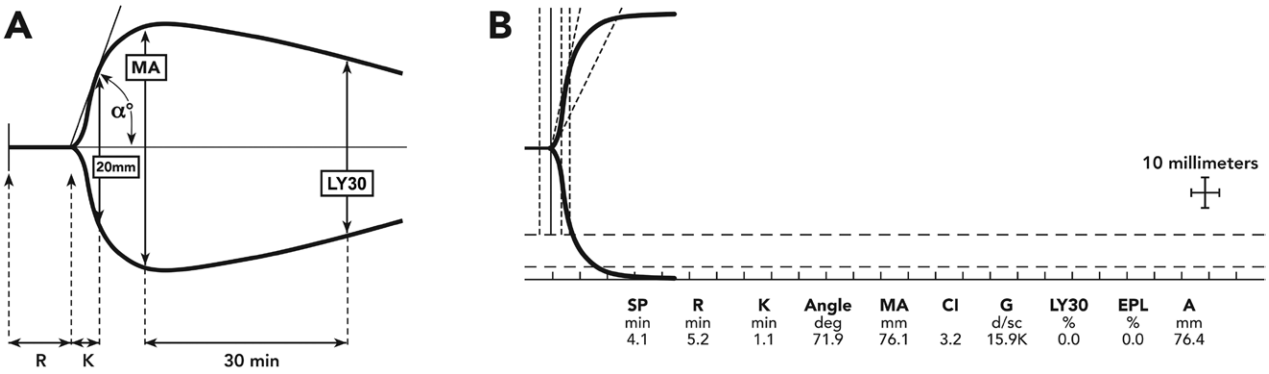
Fig. 2. CT imaging representative of typical chest trauma patient's injuries. Fractured rib, atelectasis, and pleural effusion can be seen in the CT scan. No pneumothorax is seen in this image, either. CT = computed tomography.

Discussion

There are multiple components of respiratory compromise due to chest trauma. It is important to immediately assess for catastrophic cardiogenic, noncardiogenic pulmonary, and neurogenic causes of respiratory failure, including tension pneumothorax, hemothorax, cardiac tamponade, cardiac contusion and stunning, and cervical injury.[5,6] Physical examination (vital signs, respiratory and cardiovascular examination, cervical spine instability) as well as bedside ultrasound are essential parts of the initial assesment.

In cases of multiple rib injury or flail chest, pain and inadequate respiratory efforts can increase vulnerability to atelectasis and work of breathing with decrease in the ability to clear secretions. Additionally, over the ensuing 24–48 h, pulmonary contusions can result in worsened ventilation and perfusion mismatch. Interestingly, the severity of pulmonary contusion may be less in older patients with the same degree of rib fractures. This is due to lower energy levels required to fracture the relatively brittle ribs of older patients.

Positive pressure (such as continuous positive airway pressure) to prevent atelectasis and adequate analgesia to achieve satisfactory pulmonary mechanics is key to treating rib fractures and pulmonary contusions. Severe lung injury and acute respiratory distress syndrome may necessitate intubation and mechanical ventilation.[5,6] However, maintaining spontaneous ventilation would be desirable in preventing further injury from barotrauma. If epidural analgesia is indicated, hemostatic considerations need to be considered.



Sample data:		Units
SP:		min
R:	(2–8)	min
K:	(1–3)	min
Angle:	(55–78)	deg
MA:	(51–69)	mm
CI:	(-3–3)	
G:	(4.6K–10.9K)	d/sc
LY30:	(0–8)	%
EPL:	(0–15)	%
A:		mm

Sample data:		Units
SP:	4.1	min
R:	5.2	min
K:	1.1	min
Angle:	71.9	deg
MA:	76.1	mm
CI:	3.2	
G:	15.9K	d/sc
LY30:	0.0	%
EPL:	0.0	%
A:	76.4	mm

Fig. 3. Thrombelastogram taken before insertion of the epidural catheter. R time (reaction time in seconds) is the time from the start of the test until initial clot formation, arbitrarily defined as the trace amplitude of 2 mm. K time (coagulation time in seconds), is the time taken for the trace amplitude to increase from 2 to 20 mm, and the alpha angle (in degrees) is formed between the midline and the tangent to the main body of the trace. Both describe the dynamics of clot formation. MA represents the highest amplitude of the trace. As noted in the text, the patient had regular markers of coagulation on thrombelastography, despite recent clopidogrel use. In fact, the elevated MA, reflective of clot strength, points toward a hypercoagulable state. MA = maximum amplitude.

Preexisting Antiplatelet Therapy

The literature on epidural catheter placement in the setting of antiplatelet agents is sparse.[7–10] The responsiveness to aspirin and clopidogrel and recovery of platelet function after discontinuation of treatment show considerable variability.[11–14] This may be due to patient's compliance, genetic factors, comorbidities, inflammation, plasma fibrinogen concentration, and/or comedication.[12,15] Thus, detection of platelet dysfunction may be more clinically relevant than prediction based on medication administration history.

Novel Oral Anticoagulants

Several new oral anticoagulants work by direct factor Xa (rivaroxaban and apixaban) or thrombin (dabigatran) inhibition and are given in fixed doses without lab monitoring.[16] However, severe bleeding complications, including intracerebral hemorrhage, have been reported in patients over 75 yr of age and patients with impaired renal function.[17–19] Special coagulation tests, such as anti-Xa-activity (rivaroxaban and apixaban), ecarin time or modifications of the thrombin time (Hemoclot® thrombin inhibitor test for dabigatran; Hyphen BioMed, Neuville-sur-Oise, France), are used to quantify the anticoagulant effects of these new drugs.[20] Here, viscoelastic and point-of-care tests such as certain ecarin-based thromboelastography and rotational thromboelastography tests may be helpful for timely detection of these new oral anticoagulant effects.[17,21]

Trauma-induced Coagulopathy

Trauma-induced coagulopathy is multifactorial. It is primarily driven by thrombin production from tissue injury and activation of the protein C and fibrinolytic pathways, with continued acidosis, hypothermia, hemodilution, and inflammation.[22,23] Patients may exhibit hypercoagulability from inflammation and the subsequent acute phase reaction 24–48 h after initial hemorrhage and trauma. Activated circulating cells (platelets, monocytes) and increased plasma levels of factor VIII, von Willebrand factor and fibrinogen also contribute to trauma-induced coagulopathy.

Because the fibrinolytic pathway is suppressed in the early phase of disseminated intravascular coagulopathy and sepsis, these changes in the fibrinolytic pathway can potentially be detected by viscoelastic tests.[24] Thromboelastography is predictive for both bleeding and thromboembolic events in trauma,[25,26] and ROTEM-guided hemostatic therapy (Tem International, Munich, Germany) has been associated with reduction in transfusion requirements and thrombotic events compared with conventional coagulation tests in cardiac surgery.[27,28] Thus it might be possible by using viscoelastic tests to detect trauma-induced coagulopathy early (by identifying hyperfibrinolyis and reduced clot firmness) and to discriminate between trauma-induced coagulopathy (bleeding risk) and disseminated intravascular coagulation (thrombosis risk).[25,29] Our patient did not show signs of trauma-induced coagulopathy,

Table 1. Epidural Analgesia after Clopidogrel in Trauma Patients; Clinical Considerations for Decision Making

	May Increase Bleeding Risk	May Decrease Bleeding Risk	TEG Variable to Assess	Other POC Method to Assess
Severity of Trauma	Yes (within the first days after trauma)	Yes (in acute phase later than 2–3 days after trauma)	R time, MA	ROTEM
Comorbidities:				
von Willebrand disease	Yes	No	Non	PFA-100
Diabetes mellitus	No	Yes	MA	MEA
Renal failure	Yes	No	MA	MEA
Liver cirrhosis	Yes	No	R time, MA	MEA ROTEM
Age				
> 60 yr (male)	No	Yes	R time, MA	MEA
<40yr (female)	No	Yes	R time, MA	MEA
Aspirin, NSAID	Yes	No	Platelet mapping	PFA-100 MEA
HMW heparin	Yes	No	R time	ROTEM
Warfarin (Anti-vitamin K drugs)	Yes	No	R time	ROTEM
Fluid resuscitation (with colloids)	Yes	No	MA	ROTEM
Platelet transfusion	No	Yes	MA	MEA
FFP/cryoprecipitate transfusion	No	Yes	MA	ROTEM
Time between clopidogrel and neuraxial analgesia	No	Yes	Platelet mapping	MEA ROTEM

Multiple types for each category of POC systems exist. The broad category of POC has been listed. Clinical input form result should be considered only after confirming appropriate type of POC has been performed.

FFP = fresh frozen plasma; HMW = high molecular weight (unfractionated) heparin; MA = maximum amplitude; MEA = multiple electrode aggregometry Multiplate®. VerifyNow ® may be used instead of MEA to assess platelet function; NSAIDS = nonsteroidal anti-inflammatory drug; POC = point-of-care; PFA- 100® = Platelet Function Analyzer 100; R – time = reaction time; ROTEM® = Rotational Thromboelastometry; TEG® = Thromboelastography.

but rather risk of thrombosis and hypercoagulability with supranormal maximum amplitude in TEG analysis.[26]

Point-of-care Testing

If available, viscoelastic and point-of-care platelet function tests can support decision making if platelet dysfunction is suspected (table 1).[27,30] Point-of-care platelet function analysis can be assessed with modified thromboelastography (TEG Platelet Mapping®; Haemonetics, Niles, IL), Platelet Function Analyzer PFA-100® (Siemens Healthcare Diagnostics, Eschborn, Germany), the VerifyNow® system (Accumetrics, San Diego, CA), or whole blood impedance aggregometry (Multiple Electrode Aggregometry; Multiplate® Roche Diagnostics, Mannheim, Germany).[11,12] These last two have been shown to reliably detect the antiplatelet effect of aspirin, nonopioid analgetic drugs, clopidogrel, prasugrel, and GPIIbIIIa receptor antagonists.[30]

Whole blood impedance aggregometry in particular has been useful in detecting the effects of clopigogrel, desmopressin, and tranexamic acid.[31,32] Additionally, it can predict stent thrombosis and bleeding complications in patients undergoing cardiac procedures. Thus, a "therapeutic Multiple Electrode Aggregometry window" balancing risks of bleeding and thrombosis can be defined, which would be ideal in patients with coronary stents.[11,12] As noted, thrombin time, escarin-activated clotting time, and thrombin-activated viscoelastic point-of-care tests are a few ways to reliably monitor the effects of direct thrombin inhibitors.[17,21]

We do not recommend epidural analgesia in the setting of abnormal point-of-care platelet function results or if thrombocytopenia is present. However, if aggregometry results are normal despite moderate thrombocytopenia (50,000–150,000 μl^{-1}) or a history of clopidogrel use, a sufficient platelet function can be assumed.[32]

Individualized Risk-Benefit Analysis

Our patient was at imminent risk of intubation and mechanical ventilation for acute respiratory distress. We assessed the risks and benefits, while considering variables that could affect our patient's coagulation status (table 1).

Risk of Epidural Hematoma Associated with Neuraxial Analgesia

The incidence of neuraxial hematoma after epidural anesthesia is estimated to be 1:150,000 patients. A chart review of 306 vascular surgery patients who held clopidogrel on the morning of epidural placement and another review of 130 patients without any interruption of clopidogrel showed no

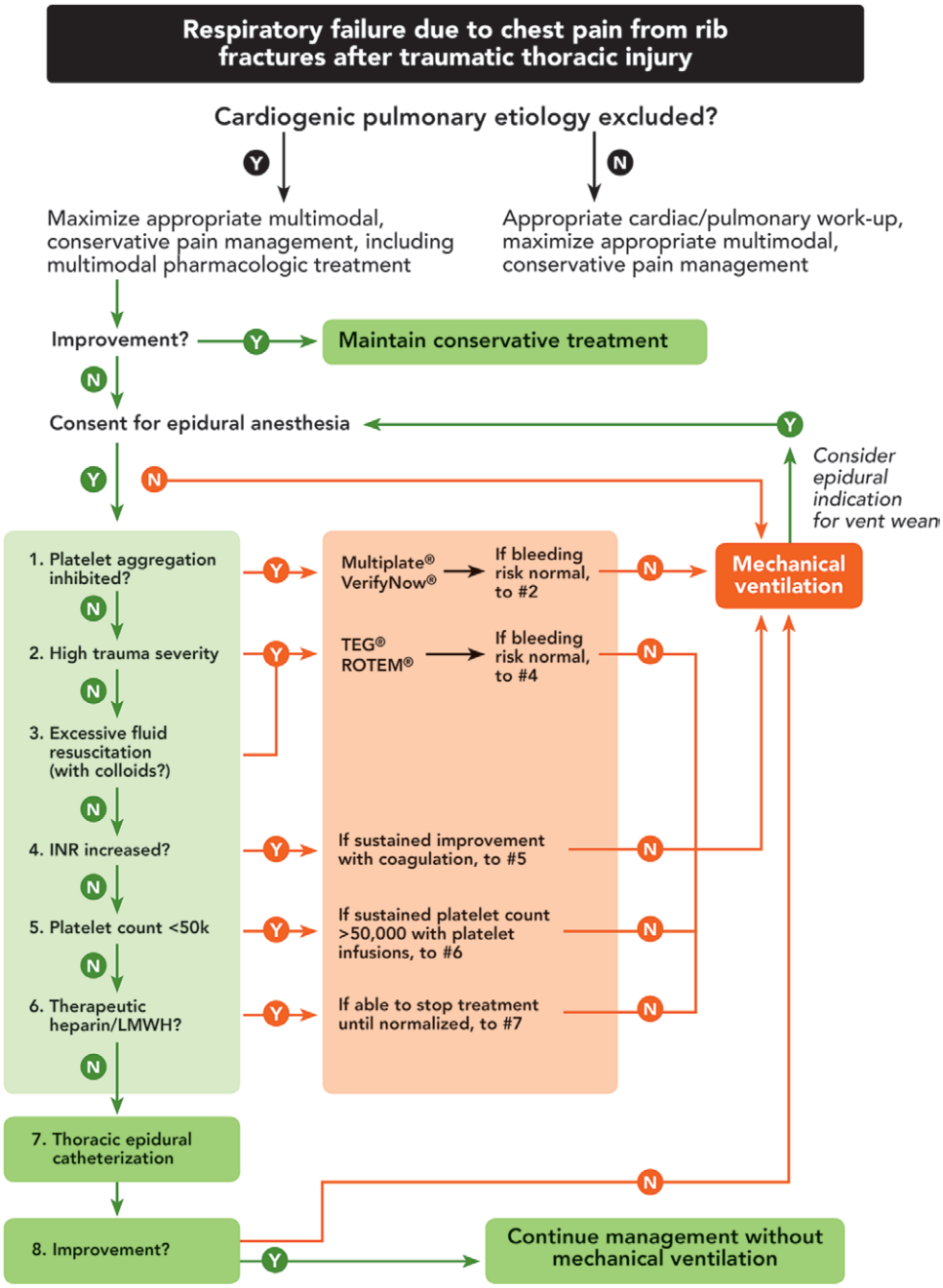


Fig. 4. Proposed algorithm for decision support. Cardiovascular, pulmonary, traumatic as well as hemostatic factors need to be considered. Conventional pain therapy must be optimized before considering epidural analgesia. If available, platelet function analysis should be performed in patients treated with antiplatelet drugs or in case of expected platelet function disorders. It is important to note that epidural catheterization and mechanical ventilation are not necessarily mutually exclusive as endpoints, and the pathways can be interconnected and synergistic. INR = International Normalized Ratio; LMWH = low molecular weight heparin; Multiplate® = MEA = multiple electrode aggregometry; ROTEM® = rotational thromboelastometry; TEG® = thromboelastography; VerifyNow® = whole blood turbidimetric platelet aggregometry.

neurological complications or epidural hematomas after epidural placement.[9,10] Extrapolating this data to evaluate the true individual risk is difficult, given the low incidence and relatively low sample size of this retrospective analysis. Guidelines for elective cases by the American Society of Regional Anesthesia and the European Society of Anesthesiologists both recommend discontinuing clopidogrel 7 days before neuraxial anesthesia.[33,34] If anesthesiologists decide not to follow these recommendations, then frequent neurologic checks are essential to identify early an epidural hematoma. In addition, we recommend that an epidural catheter without metal coils should be used which can stay *in situ* during

magnetic resonance imaging if needed. An appropriate surgical consultant needs to be immediately consulted if emergent spinal decompression is required.

Risk of Mechanical Ventilation

Ninety percent of ICU-acquired pneumonias occur during mechanical ventilation and half of ventilator-associated pneumonias develop within 4 days of intubation. The incidence of ventilator-associated pneumonias ranges from 10% to 25%, with mortality between 10% to 40%, when on average adding 6 ICU and 18 hospital days to patient admissions.[35,36] Mechanical ventilation for 48 h is a significant risk factor for developing stress ulcer-related bleeding, venous thromboemboli, and pressure ulcers.[37] There is often increased difficulty after neurologic exams and delay in ambulation and physical therapy during mechanical ventilation, and immobility-related adverse effects need to be taken into account.

Risk of Stent Thrombosis after Coronary Artery Stent Implantation

Discontinuation of dual antiplatelet therapy within 3 months of bare metal stent placement or 12 months after drug-eluting stent implantation is associated with increased risk of stent thrombosis. Furthermore, the proinflammatory state after major trauma or surgery itself is a considerable risk factor for stent thrombosis due to an acute phase reaction, marked by increased production of C-reactive protein, ferritin, and especially fibrinogen. In pregnancy and long-standing diabetes, this has been shown to compensate for thrombocytopenia or platelet dysfunction, resulting in low responsiveness to antiplatelet therapy.[31,38,39] Accordingly, point-of-care tests may provide individualized therapy to reduce the risk of spinal bleeding and stent thrombosis.[13,24,31]

Alternative Techniques for Pain Management

Multimodal conservative pain management with intravenous and oral analgesia using opioids, nonsteroidal anti-inflammatory agents, and/or acetaminophen is ideal if tolerated from a respiratory standpoint. Of the nonpharmacologic interventions, thoracic paravertebral catheters have improved pain and pulmonary function for patients with rib fractures. However, due to both extension from the paravertebral space and inadvertent epidural placement, a similar bleeding risk profile exists for both techniques.[40,41] With the use of real-time ultrasound, the risk of misplacement may have to be reassessed in the future.

Interpleural catheters have also demonstrated effectivenes, although the insertion site can be a significant source of discomfort, and especially with bilateral catheters, the risk of local anesthetic toxicity must be weighed.[42] Similarly, rib blockades can be considered, but multiple, repeated blocks carry concern for local anesthetic toxicity. Surgical fixation of ribs in patients with severe flail chest may improve pulmonary function while decreasing days of mechanical ventilation, mortality, and even cost of care. However, most patients are already mechanically ventilated with this degree of injury. The procedure is not without risk, with up to a 10% reoperative rate due to hardware causing pain.[43] Finally, patients with gross, irreversible coagulation abnormalities or difficulty with neuraxial analgesia placement may require mechanical ventilation and sedation.

Knowledge Gap

The clinical scenario of a patient on antiplatelet medications with chest trauma induced acute respiratory failure is complex. Most guidelines on elective regional anesthesia in patients are primarily based on the half-life time of the drugs and of limited help in this setting. Thus, the decision to perform unplanned neuraxial blockades in patients with altered hemostasis needs careful assessment of individual risks and benefits.

Recent literature on patients with severe trauma or cardiac procedures demonstrated that functional point-of-care testing of hemostasis may be helpful in both risk-benefit analysis and guidance of hemostatic therapy.[27,30] The authors are aware that the evidence for using viscoelastic and aggregometric tests for point-of-care diagnostics in neuraxial anesthesia is low. Further evaluation and validation is needed. However, meaningful, prospective, randomized controlled trials are not feasible due to the low incidence of spinal hematoma after neuraxial anesthesia.[33,34] Though point-of-care testing of hemostasis is not uniformly available, the authors tried to provide a simplified, rational algorithm to guide risk-benefit analysis for epidural placement in thoracic trauma patients (fig. 4). This will also need validation in future clinical studies.

Algorithm for Decision Support

In patients presenting with chest trauma and pain-related respiratory distress, the benefits of epidural placement to avoid prolonged mechanical ventilation may outweigh the risks. An algorithm to provide decision supports is proposed (fig. 4). Initially, one must exclude primary cardiogenic or pulmonary etiology. If multimodal systemic analgesic therapy is ineffective, the patient's coagulation status must be assessed. Ultimately, patients' levels of pain and associated respiratory distress, medical comorbidities, preadmission medications, as well as the available tests to characterize and correct coagulation status must be assessed. This determines whether regional anesthesia with spontaneous ventilation or mechanical ventilation with parenteral analgesia and sedation is required. Additionally, if continued respiratory failure on mechanical ventilation is due to impaired respiratory mechanics from rib fracture pain, epidural analgesia should be considered to help decrease sedation and improve mechanical wean.

The authors thank Edward Bittner, M.D., Ph.D. (Associate Director for Education, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts), who was also staff intensivist during care of the patient and who reviewed the case scenario.

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