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Review article

Perioperative pulmonary embolism: diagnosis and anesthetic management

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Abstract All perioperative patients, but especially trauma victims and those undergoing prostate or orthopedic surgery, are at increased risk of venous thromboembolism. Patients at highest risk include those with malignancy, immobility, and obesity; those who smoke; and those taking oral contraceptives, hormone replacement therapy, or antipsychotic medications. Dyspnea, anxiety, and tachypnea are the most common presenting symptoms in awake patients, and hypotension, tachycardia, hypoxemia, and decreased end-tidal CO_2 are the most common findings in patients receiving general anesthesia. The presence of shock and right ventricular failure are associated with adverse outcomes. Helical computed tomographic scanning is the preferred definitive diagnostic study, but transesophageal echocardiography may be valuable in making a presumptive diagnosis in the operating room. Early diagnosis allows supportive therapy and possible anticoagulation (in some cases, to be started before the conclusion of surgery).

1. Introduction

Surgery puts patients at increased risk for pulmonary embolism (PE). Anesthesiologists may find themselves responsible for the diagnosis and management of this sometimes fatal disorder. Further, the diagnosis is often one of exclusion and may be obscured intraoperatively by much more common disorders, including bleeding and infection. The ongoing surgical procedure may limit initial management options.

The diagnosis and treatment of PE in medical patients recently was reviewed by Wood [1] and Tapson [2]. Pulmonary embolism presents different challenges in surgical patients. At the time of surgery, PE often first presents with hemodynamic instability and it is more likely to follow a rapid course, leading to death within several hours. Prompt diagnosis and management, however, may reduce morbidity and mortality.

2. Incidence in surgical patients

There is as great as a fivefold increase in the incidence of PE during and after surgery [3,4]. Surgical patients have many patient-specific risk factors for PE, in addition to risk factors unique to the perioperative experience, including the acute inflammatory reaction caused by tissue trauma, activation of the clotting cascade, and immobilization/venous stasis. In Goldhaber et al.'s series, 50% of the perioperative patients who suffered perioperative PE had received thromboembolism prophylaxis [5]. Table 1 shows

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Table 1 Incidence of perioperative pulmonary embolus (PE) by type of surgical procedure

Surgical population	Incidence of PE	Incidence of fatal PE
General surgery	1.6% (average) [4,6]	0.9% (average) [4]
Thoracic	1.5%-2% [109,110]	0.34%-1.2% [13,110]
Abdominal	0.32%-1.0% [13,111]	0.03%-0.4% [13,111]
Laparoscopic	0.06%-0.9% [13-16]	0-0.02% [15,16]
Vascular	0.4%-0.7% [112,113]	0.1%-0.2% [112,113]
Head and neck	0.4%-0.44% [114,115]	0.06% [114]
Gynecologic	0.3%-4.1% [116]	0.4% [3]
Ortho: THA	0.7%-30% [4]	0.1%-0.4% [4]
Ortho: TKA	1.8%-7% [4]	0.2%-0.7% [4]
Ortho: hip fracture repair	4.3%-24% [4]	3.6%-12.9% [4]
Urologic	0.9%-1.1% [117-119]	< 0.2% [4]
Neurosurgical	0-4% [120-122]	0.13-1% [121,123,124]
Trauma	2.3%-6.2% [105,125]	0.4-2% [4]
Acute SCI	4.6%-9% [126,127]	3%-5% [128-130]

The incidence of pulmonary embolism during and following hospitalization in patients undergoing various types of surgical procedures, including patients with and without preoperative deep vein thrombosis (DVT) prophylaxis.
THA = total hip arthroplasty, TKA = total knee arthroplasty, SCI = spinal cord injury.

the incidence of PE associated with various surgical procedures. Pulmonary embolism occurs in approximately 0.3% to 1.6% of the general surgical population [3,4,6,7]. In 2009, Beyer et al. reported that the incidence of PE after prostate procedures was 5.8% [8]. The incidence of PE has been quoted as 0.7% to 30% after all orthopedic surgical procedures, and 4.3% to 24% following hip fracture repair, primarily as a result of the location of the surgical procedure, which may distort the femoral vein, leading to impaired venous return and stasis [9]. Most series do not distinguish between emboli occurring during and after surgery, but Koessler et al. reviewed 4 series of patients undergoing total hip arthroplasty and found that the incidence of symptomatic intraoperative PE was between 0.6% and 10% [10]. Mortality associated with perioperative PE is as high as 12.9% in patients presenting for hip fracture repair [4,11]. However, both Kerkez et al. and Milbrink and Bergqvist recently found a much lower incidence of symptomatic emboli, approximately 0.25%, in patients receiving thromboembolism prophylaxis following hip fracture surgery [7,12].

In contrast to the high rate of perioperative PE in orthopedic patients, laparoscopic procedures have been associated with a low incidence of both non-fatal and fatal PE [13-16]. This decrease has been hypothesized to occur secondary to less surgical trauma, earlier ambulation, as well as a less pronounced prothrombotic state in laparoscopic than open surgical procedures [17].

Some of the variation in incidence of postoperative PE over the past 10 years may be attributed to advances in the detection of smaller and more peripheral emboli. Auer et al. [18] found that the incidence of postoperative PE increased from 2.3 to 9.3 per 1,000 in unselected cancer patients during the years from 2000 to 2005. This increase correlated with an increase in the use of spiral (helical) computed tomographic (CT) scans from 6.6 scans per 1,000 postoperative patients in 2000 to 45 scans per 1,000 postoperative patients in 2005, and it was attributed almost entirely to improved detection. The increased detection was limited to segmental and subsegmental emboli. Some 10.7% of the patients diagnosed in 2005 were asymptomatic. The incidence of fatal PE in this series remained constant at 0.4 per 1,000 patients each year, implying that there was no change in the incidence of severe emboli [18].

3. Pathophysiology

3.1. Changes in pulmonary function and gas exchange

Abnormalities in respiratory function and pulmonary gas exchange are some of the first changes seen when venous emboli lodge in the lungs. They have been attributed to an increase in alveolar dead space, or more directly to right-to-left shunting and V/Q mismatch, which may be consequences of the physical obstruction to blood flow caused by the emboli themselves. As blood flow is shunted away from the obstructed pulmonary arteries (PAs), it then causes overperfusion of the rest of the lung tissue, leading to edema, loss of surfactant, and alveolar hemorrhage. The resulting atelectasis develops acutely but may remain long after the emboli themselves resolve and the lung is reperfused [1]. Hypoxia due to pulmonary changes may be much more severe in the presence of a probe-patent foramen ovale, opened by the elevated right atrial (RA) pressure and causing a large interatrial shunt. In patients with low cardiac output (CO), low mixed venous pO_2 may exacerbate the effects of shunt or V/Q mismatch on arterial oxygenation. However, augmentation of CO with inotropes also may decrease pO_2

by increasing shunt blood flow. Regional hypocarbia may lead to bronchoconstriction, as may humoral mediators such as serotonin released from platelet-rich emboli [19].

3.2. Circulatory changes

The initial hemodynamic insult with PE is obstruction to blood flow caused by emboli in the pulmonary vasculature and pulmonary outflow tract, leading to an acute increase in right ventricular (RV) impedance. Right ventricular outflow impedance also may be increased by preexisting pulmonary disease, as well as by neural reflexes and the release of pulmonary vasoconstrictors into the circulation. Pulmonary vasoconstrictors such as serotonin and platelet-activating factor originate from platelets trapped in the emboli themselves. Vasoactive peptides such as activated complement factors 3 and 5 come from plasma, and histamine comes from tissue mast cells [1]. The acute increase in pulmonary vascular resistance and RV afterload may start the cycle of deleterious circulatory changes shown in Fig. 1.

Because of its geometry, the RV is much more sensitive to pressure than to volume loads. Therefore, increases in pressure load will lead to significant decreases in RV stroke volume (SV). To maintain CO, the body's initial response is catecholamine-mediated tachycardia and an increase in RA pressure and RV preload, in an attempt to return SV to normal. However, increasing RV preload often leads primarily to RV dilation and subsequent leftward shift in the interventricular septum, limiting left ventricular (LV) filling. With continued increase in RV afterload and pressure, and especially in the face of RV ischemia, the RV begins to fail and CO begins to decrease. As the RV pumps less blood through the constricted pulmonary vessels, LV preload will decrease, decreasing LV output to the systemic circulation. Initially catecholamine-induced vasoconstriction will increase systemic vascular resistance and maintain systemic arterial pressure (BP). However, further decrease in CO leads to systemic hypotension.

Right ventricular dilation and increased RV afterload both lead to an increase in the RV wall stress, which can be determined by Laplace's Law, as applied to thin-walled structures such as the RV [20]:

$$\text{Wall stress} = \frac{\text{pressure x radius}}{\text{2 x wall thickness}}$$

Since wall stress is an important determinant of RV oxygen demand, increased wall stress, especially if coupled with systemic hypotension and decreased coronary perfusion pressure (CPP), may precipitate RV ischemia, and even infarction [21].

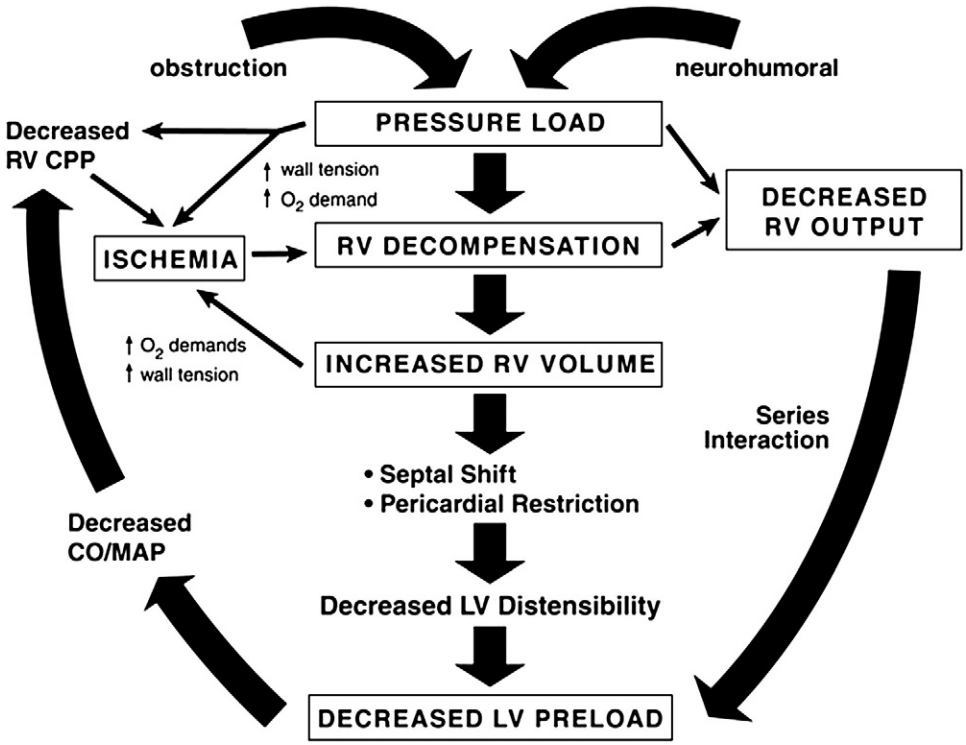

Fig. 1 Pathophysiology of major pulmonary embolus. Effects of increase in pulmonary vascular resistance and right ventricular (RV) afterload. CPP = coronary perfusion pressure, CO/MAP = cardiac output/mean arterial pressure, LV = left ventricle. From: Wood KE. Pulmonary embolism: review of a pathophysiologic approach to the golden hour of a hemodynamically significant pulmonary embolism. Chest 2002;121:877-905 [1], with permission.

Table 2 Hemodynamic consequences of a major pulmonary embolus compared with common alternative diagnoses

	Blood pressure	Right atrial pressure	Pulmonary artery pressure	Pulmonary vascular resistance	Left atrial pressure	Cardiac output	Systemic vascular resistance
Hypovolemia	↓	↓	↓	±	↓	↓	↑
Sepsis	↓	↓	↓	±	↓	↑	↓↓
Left ventricular failure	↓	↑	↑	±	↑↑	↓	↑
Pulmonary embolism	↓	↑	↑↑	↑↑	↓	↓	↑

↑increase, ↑↑ large increase, ↓decrease, ↓↓ large decrease, ± small or no change.

The hemodynamic changes associated with PE are summarized and compared with those of other common causes of hypotension (Table 2).

Table 3 Patient risk factors for venous thromboembolism and pulmonary embolism

Hereditary
- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden
- Prothrombin gene deficiency

Acquired
- Advanced age
- Cancer
- Reduced mobility
- Acute medical illness (CHF, respiratory failure)
- Inflammatory bowel disease
- Nephrotic syndrome
- Pregnancy/postpartum period
- Central venous catheterization
- Trauma
- Spinal cord injury
- Obesity
- Previous venous thromboembolism
- Tobacco use

Medications
- Heparins
- Hormone replacement therapy
- Oral contraceptives
- Chemotherapy
- Antipsychotics

Surgery
- "Major surgery"-loosely defined (includes most open abdominal and thoracic procedures)
- Fracture (hip or leg)
- Hip or knee replacement
- General anesthesia (when compared with epidural/spinal for lower abdominal and lower extremity surgery)

Adapted from: Tapson VF. Acute pulmonary embolism. N Engl J Med 2008;358:1037-52 [2] (© 2008, Massachusetts Medical Society, all rights reserved), and Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation 2003;107(23 Suppl 1):I9-I16 [131], with permission.
CHF = congestive heart failure.

4. Patient risk factors

More than 100 years ago, Virchow described his now famous triad of risk factors for venous thromboembolism (VTE): venous stasis, endothelial damage, and a hypercoagulable state [22]. All risk factors for PE may in some way be traced back to this central concept. Table 3 provides an extensive list of risk factors, and it is clear that many of these risks are present in the surgical patient. Patients with malignancy deserve special attention. They have increased risks associated with malignancy secondary to induction of a hypercoagulable state caused by both hormones released from the tumor and certain chemotherapeutic agents. Patients with cancer are also affected by reduced mobility, frequent presence of indwelling central venous catheters, as well as possible venous obstruction from tumor. Cancer is such a strong risk factor for VTE that a recent meta-analysis by Carrier et al. showed that cancer patients have 30 VTE events per 100 patient years compared with 12.8 events per 100 patient years in the general population [23], and the rate of PE in cancer patients with an indwelling central venous catheter has been estimated at 15% to 25% [24]. A prospective study by Goldhaber et al. showed that obesity (BMI > 29 kg/m^2) and smoking (> 35 cigarettes/day) were independent risk factors of PE in women, with a relative risk of PE of 2.9 and 3.3, respectively [25].

Certain medications also may induce a hypercoagulable state in patients. Specifically, the risk of PE in women using second-generation oral contraceptives is three times greater than in non-users [26], and hormone replacement therapy is associated with an approximately twofold increase in the risk of PE [27-29]. A recent study by Lacut et al. showed a 3.5-fold increase in the rate of VTE in patients taking antipsychotic medications [30].

4.1. Effects of anesthetic on risk

The choice of anesthetic technique may have a profound impact on the patient's risk for VTE. A meta-analysis by Rodgers et al. comparing epidural anesthesia (either as the primary anesthetic or as an adjunct to general anesthesia) with general anesthesia alone, showed a 44% and 55% reduction in the rates of deep vein thrombosis (DVT) and PE, respectively, for the epidural group [31]. A second meta-

analysis investigated the impact of continuous lumbar epidural on thromboembolic complications in hip surgery, knee surgery, prostatectomy, and lower extremity vascular surgery, finding a 34% reduction in events in the epidural group [32]. However, when this same meta-analysis looked at the impact of thoracic epidurals in major abdominal and thoracic surgery, no significant difference was seen in the epidural group. This difference in epidural effect is presumed to be caused by the fact that thoracic epidurals have a less profound effect on lower extremity blood flow and venous stasis than lumbar epidurals [32].

5. Diagnosis

5.1. Physical findings

While the common presenting symptoms in awake patients are often helpful in the initial diagnosis of PE, they are masked in the anesthetized, mechanically ventilated patient. The anesthesiologist then must rely on other findings that may still appear in unconscious patients. Hypotension and tachycardia are the classic intraoperative findings associated with PE [33].

Kasper et al. found that 59% of hospitalized patients with major PE presented with significant hemodynamic instability–18% presenting in cardiac arrest and 10% with hypotension requiring vasopressor support [34]. Prominent physical findings that may be obtained by the anesthesiologist include an arterial pulse that is sharp and of small volume, tachycardia (HR > 100 bpm), elevated jugular venous pressure, a gallop rhythm at the left sternal edge, and an accentuated second heart sound [21]. Wheezing has been cited frequently as a physical finding that may be present in acute PE. However, wheezing is present to the same extent in patients with proven PE and those in whom PE has been ruled out [35] Table 4.

The presence of shock is an early and reliable predictor of mortality in patients with acute PE, regardless of whether the shock is caused primarily by a massive PE or a smaller PE in patients with severe preexisting cardiopulmonary disease. Kucher et al. found an almost fourfold increase in all-cause, 90-day mortality in patients presenting in shock compared with normotensive patients [36]. Toosi et al. found that a "shock index" (HR/systolic blood pressure) > 1 had a significant positive association with inhospital mortality and was helpful in triaging patients with acute PE into high and low-risk groups [37]. Furthermore, patients presenting in shock are much more likely to die in the first hour [1]; diagnosis and institution of therapy must be much more rapid than for hemodynamically stable patients.

Table 4 Clinical findings at diagnosis in patients with major pulmonary embolism

Dyspnea	96%
Tachycardia	71%
Acute onset of symptoms (< 48 hrs)	70%
Age > 65 yrs	52%
Syncope	35%
Arterial hypotension (SBP < 90 mmHg)	34%

Adapted from Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol 1997;30:1165-71, with permission.
SBP = systolic blood pressure.

5.2. Intraoperative diagnostic tests

In the best of circumstances, PE is a diagnosis of exclusion. During and after anesthesia and surgery, diagnosis may be even more difficult. However, common intraoperative monitors and diagnostic studies, perhaps modified slightly and coupled with a high index of suspicion, may lead to at least a presumptive diagnosis, even during surgery. This early diagnosis is invaluable in planning management and reducing morbidity.

5.2.1. Electrocardiography

Most patients with PE exhibit some abnormalities on electrocardiography (ECG). Geibel et al. found sinus tachycardia and atrial arrhythmias in 83% of patients with a confirmed diagnosis of PE; atrial arrhythmias, in particular, were associated with a higher mortality rate [38]. Other common ECG findings associated with PE are ST segment and T wave abnormalities. Non-specific ST changes, ST elevation and depression, or T wave inversion, are found in approximately 50% of patients. Complete right bundle branch block and T wave inversions in the precordial leads are the findings that correlate best with severity of PE [38-40].

The ECG findings of acute cor pulmonale, such as right-axis deviation, complete or incomplete right bundle branch block, the $S_1Q_3T_3$ pattern (Fig. 2), P-pulmonale, and anterior T wave inversions are associated with RV dysfunction and correlated strongly with short-term and 30-day mortality [38,41].

However, serious rhythm disturbances are uncommon. Atrial fibrillation/flutter; first, second, or third degree heart block; as well as ventricular dysrhythmias, are present in less than 5% to 10% of patients [42].

5.2.2. Arterial blood gases

The usual arterial blood gas (ABG) changes found in spontaneously breathing patients with PE are hypoxemia, respiratory alkalosis, and hypocapnea. Systemic arterial hypoxemia is the most sensitive manifestation of PE and is perhaps the only ABG abnormality in patients with obstruction of 25% or less [43]. In patients with no prior cardiopulmonary disease, room air PO_2 was less than 80 mmHg in 74% [42], and the severity of the PE had an inverse linear relationship to the arterial PO2 [43]. Patients with a

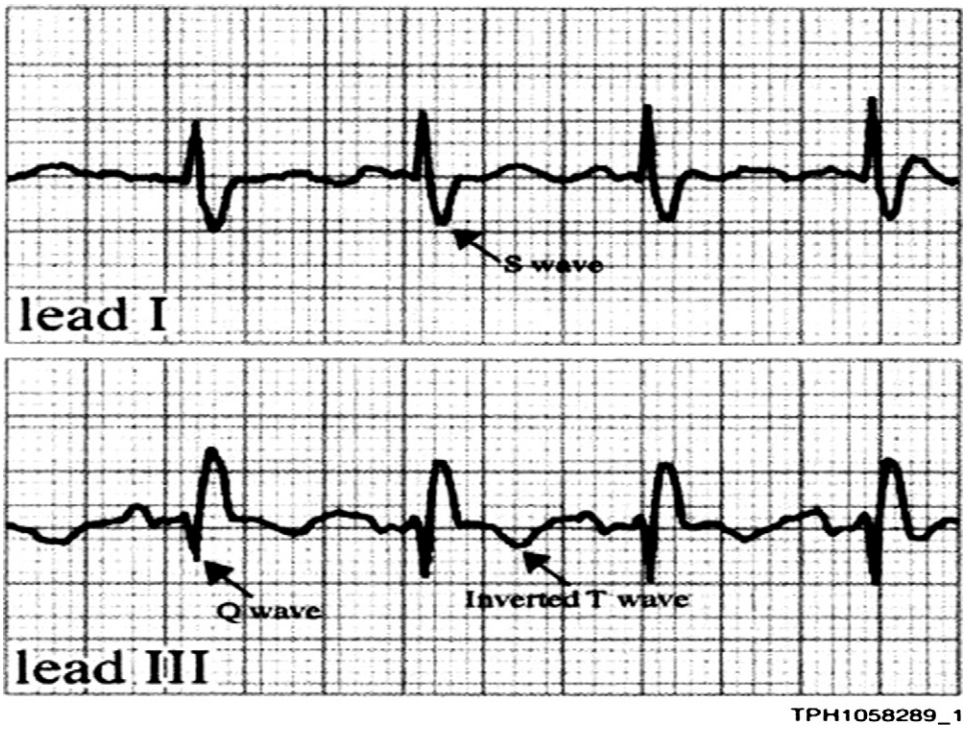

Fig. 2 S1Q3T3 pattern. From: Stead LG, Stead SM, Kaufman MS. First Aid for the Emergency Medicine Clerkship: A Student Guide. New York: McGraw-Hill; 2001. p. 118 [132], with permission.

room air oxygen saturation of less than 95% at the time of diagnosis had a higher incidence of complications [44].

5.2.3. Physiologic dead space

An increase in physiologic dead space is almost invariably associated with pulmonary thromboembolism. In a small study of 12 surgical patients with PE, Anderson et al. found that dead space showed 100% sensitivity and 89% specificity in predicting the diagnosis [45]. The ratio of physiologic dead space to tidal volume may be calculated using the Bohr equation:

$$V_{d\ phys} = V_T[(PaCO_2 - PeCO_2)/PaCO_2]$$

where $V_{d\ phys}$ is the physiologic dead space, V_T is the tidal volume, $PeCO_2$ is the mixed expired PCO_2, and $PaCO_2$ is the arterial PCO_2. Arterial PCO_2 may be measured directly. However, to determine the mixed expired PCO_2, exhaled PCO_2 must usually be analyzed in a mixing box, a Douglas bag must be used, or the mixed expired PCO_2 must be calculated by commercially available devices that integrate instantaneous PCO_2 over an entire breath (Nico monitor; Nova Metrix Medical Systems, Wallingford, CT, USA). None of these devices is readily available in most operating rooms (ORs).

However, several authors have discussed practical methods to at least estimate the mixed expired PCO_2 or the physiologic dead space. Most recently, in 2007, Badel and Loeb described a simple method to estimate mixed expired PCO_2 using a standard anesthesia breathing circuit [46]. They threaded a "side stream" PCO_2 sampling line into the ventilator bellows of the anesthesia machine through an adapter placed between the bellows and the breathing circuit, and used this sampling line to measure PCO_2 of the gas within the bellows, which corresponded to the mixed exhaled PCO_2 within ± 12%, even with high fresh gas flows. At fresh gas flows less than 2,000 mL/min, the accuracy of the measurement was even greater. Using this device along with measured arterial PCO_2, the V_d/V_t and especially changes in V_d/V_t may be calculated intraoperatively.

In 1976, Sahn et al. discussed a simple but more empirical method of predicting elevations in dead space, assuming normal CO_2 production. Using their method, in an adult, if V_e x $PaCO_2$ > 8 x (patient body weight in kg), it is likely that the dead space is elevated [47].

5.2.4. Laboratory studies

D-dimer, and especially the enzyme-linked immunoabsorbent assay (ELISA), is a sensitive but very nonspecific test for PE. The ELISA assay has a sensitivity of 96% to 98%, but it also may be positive in conditions unrelated to PE, including infection, cancer, trauma, surgery itself, and other inflammatory states. Therefore, a negative d-dimer study is helpful in ruling out PE in patients with a low clinical suspicion. However, an elevated d-dimer is of little help in supporting a diagnosis of PE or estimating its severity [2].

Serum troponin I and troponin T are elevated in less than 50% of patients with an acute, moderate to large PE, so they are not very helpful in making this diagnosis. However, elevation of these markers is associated with adverse

outcomes, including death, and the need for catecholamines and resuscitation [2,48].

Finally, the levels of brain naturetic peptide (BNP) may be elevated in PE, but these are likely caused by RV dilation and thus are also elevated in many other conditions, such as heart failure, which could cause ventricular dilation [49,50]. Sohne et al. found a sensitivity and specificity of only 60% and 62%, respectively, for BNP in hemodynamically stable patients with acute PE [51], limiting its diagnostic usefulness.

5.2.5. Chest radiograph

Elliott et al. found that cardiomegaly is the most common finding on chest radiograph in patients with PE [52]. Although the chest radiograph is usually not very helpful in establishing a diagnosis of PE, it may either support or rule out alternative causes of hypoxemia and hypotension, such as pneumothorax, pleural effusion, pneumonia, atelectasis, aspiration, or heart failure, which were found on the chest radiograph in more than 50% of patients with a presentation concerning for PE [42].

5.2.6. Confirmatory diagnostic tests

If the patient is not actually undergoing surgery and is hemodynamically stable, several options are available to confirm or rule out PE. Traditionally, V/Q scan has been considered the first-line test. However, the vast majority of V/Q scans in the 1990 Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study were non-diagnostic, with only 15% being "normal" and 13% being "high probability" [53], leaving 72% as "indeterminant". More recently, single photon emission computed tomography (SPECT) imaging has improved the predictive value of V/Q scans, with only 1% now nondiagnostic [54].

Angiography has long been considered the "gold standard" for the diagnosis of PE. It is expensive, invasive, and not uniformly available. It is also not without risk. Stein et al. showed a 4% incidence of major complications (including death and renal failure) in the intensive care population undergoing angiography [55].

Spiral, or helical, CT scanning continues to gain favor because it is noninvasive, comparably inexpensive, and readily available. The overall sensitivity for detecting PE with spiral CT is approximately 85% [56,57]. A pooled analysis of several large series by Wood [1] showed that spiral CT is considerably more sensitive (94%) and specific (94%) for detecting PE in the central arteries. In cases of PE that are associated with hemodynamic instability or evidence of RV overload, the sensitivity and specificity of spiral CT approach 100% [58-60]. Pooled analysis of more than 2,500 patients by Schoepf et al. showed greater than 99% negative predictive value associated with a normal spiral CT scan [61]. Auer et al. in 2009, showed that spiral CT scanning significantly increased the likelihood of a diagnosis of segmental and subsegmental PE in postoperative cancer patients. As was mentioned earlier, the study was so sensitive in their series that 10.7% of patients in whom spiral CT scan diagnosed peripheral PE were asymptomatic [18].

Echocardiography is not the preferred test to confirm the presence of PE. Rosenberger et al. showed that an embolus was visible on transesophageal echocardiography (TEE) in only 26% of patients with severe PE [62]. However, TEE may be particularly useful to the anesthesiologist as it is readily available and may be performed in the OR without interrupting the surgical procedure. The speed and accuracy of TEE renders it an attractive choice, as shown by Pruszczyk et al. These researchers showed that, in an average examination time of 9.6 minutes, TEE had a sensitivity of 80.5% and a specificity of 97.2% in a patient population with clinical suspicion of PE and evidence of RV strain [58]. Pruszczyk et al. also showed that TEE compared favorably with spiral CT in establishing the diagnosis of acute, central PE [58,63]. Rosenberger et al. found that TEE detected RV dysfunction in 96%, tricuspid regurgitation in 50%, and leftward atrial septal bowing in 98% of patients with PE that was severe enough to require surgery [62].

In assessment of PE, RV dilation is the most common finding on TEE. However, at least 30% obstruction of the pulmonary vasculature is required to produce RV dilation [1]. Further, RV dilation may result from other disease states such as cor pulmonale with pulmonary hypertension, RV infarction, or chronic/recurrent PE [64]. Kasper et al. showed that RV dilation associated with cor pulmonale or chronic/recurrent PE was associated with RV hypertrophy, while RV dilation from acute PE or RV infarct was not. In addition, ventricular septal shift is commonly seen in acute PE and not in RV infarct [64]. Table 5 highlights some of the more common echocardiographic findings associated with PE [65,66]. Moderate to severe RV hypokinesis following PE, with an RV/LV diastolic diameter ratio > 1 on TEE, has been associated with significantly higher in hospital morbidity [37,67].

Table 5 Echocardiographic findings associated with pulmonary embolism

RV/LV end-diastolic diameter ratio > 0.7
RV/LV area ratio > 0.66
RV end-diastolic diameter > 27 mm
"McConnell sign" *
Septal shift
Tricuspid regurgitation > 270 cm/sec

Adapted from Lodato JA, Ward RP, Lang RM. Echocardiographic predictors of pulmonary embolism in patients referred for helical CT. Echocardiography 2008;25:584-90 [65], with permission; and Nazeyrollas P, Metz D, Chapoutot L, et al. Diagnostic accuracy of echocardiography-Doppler in acute pulmonary embolism. Int J Cardiol 1995;47:273-80 [66], with permission.

RV/LV = right ventricular/left ventricular.

* Presence of RV-free wall hypokinesis or akinesis coupled with RV apex normokinesis or hyperkinesis.

In addition to aiding in the diagnosis of PE, TEE is useful in establishing alternative diagnoses such as aortic dissection, pericardial disease, hypovolemia, myocardial dysfunction/infarction, and valvular insufficiency [1,63], as well as guiding therapy in the resuscitation of hemodynamically unstable patients [68].

6. Prophylaxis of deep vein thrombosis/ pulmonary embolism

6.1. Pharmacologic prophylaxis

The 2008 guidelines for the prevention of VTE by the American College of Chest Physicians recommend that patients undergoing major general surgery receive thromboprophylaxis in the form of either low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (LDUH), or fondaparinux. Patients undergoing major gynecologic or major, open urologic procedures should receive either LMWH, LDUH, fondaparinux, or intermittent pneumatic compression. All major trauma patients and patients with spinal cord injury, as well as other spinal and neurosurgery patients with risk factors for thromboembolism, should have mechanical prophylaxis with sequential compression during surgery, and then pharmacoprophylaxis begun postoperatively [4].

Orthopedic surgery patients are at a notably high risk for perioperative VTE and as such prophylaxis in this group deserves special attention. It is recommended that patients undergoing elective hip or knee replacement receive either LMWH, fondaparinux, or warfarin (with INR 2-3), while patients having hip fracture repair should receive either LMWH, fondaparinux, warfarin, or LDUH [4]. Prophylaxis with warfarin should begin the night before surgery. Prophylaxis with LMWH or LDUH should begin either 12 hours before surgery or 4 to 24 hours postoperatively. For patients receiving fondaparinux, therapy should begin 6 to 8 hours postoperatively. Each of these groups of patients should receive thromboprophylaxis for a minimum of 10 days postoperatively, and patients undergoing hip arthroplasty or hip fracture repair should continue this therapy for up to 35 days [4].

Low-molecular-weight heparin has become a popular choice for VTE prophylaxis because, in most instances, it does not require laboratory monitoring of levels [2,4,69]. There is less need for monitoring because the antithrombotic response to weight-based dosing is more predictable than with unfractionated heparin (UFH), owing to the smaller molecular size of LMWH. The smaller size results in less charge-related protein binding and improved subcutaneous bioavailability [69]. Because LMWH is cleared by the kidneys, it is recommended that UFH be used instead of LMWH in patients with creatinine clearance < 30 mL/min. If LMWH is used in this patient population, it is recommended that lower doses be used and/or anti-Xa levels be followed [4,69]. Less predictable bioavailability also may be encountered in morbidly obese (> 150 kg), very thin (< 40 kg), or pregnant patients, and therefore anti-Xa levels should be considered in these patients as well [69].

Fondaparinux is a relatively new anticoagulant that binds antithrombin III, increases its activity, and inhibits factor Xa but has no direct activity against thrombin. It is rapidly absorbed, has near 100% bioavailability, and a half-life of 15 hours that renders it suitable for once daily dosing [70,71]. Fondaparinux is also associated with a lower incidence of heparin-induced thrombocytopenia [72]. Fondaparinux, like LMWH, is eliminated by the kidneys and similar precautions should be taken in dosing for patients with renal failure [4,73].

6.2. Mechanical prophylaxis

While it is generally less efficacious than pharmacologic means of prophylaxis [74], mechanical prophylaxis such as intermittent pneumatic compression devices, reduces the incidence of VTE by as much as 60% when compared with no prophylaxis [75,76]. Mechanical prophylaxis is the thromboprophylaxis method of choice in patients with a high risk of bleeding or for patients in whom bleeding would be catastrophic, such as neurosurgical patients [4].

6.2.1. Vena cava filters

The role of vena cava filters in the prophylaxis of PE in high-risk patients, such as those with recent trauma, is controversial. While some studies have suggested that filters reduce the incidence of PE [77,78], no reduction in mortality has been shown, and the presence of a vena cava filter increases the risk of recurrent DVT by as much as 9% [79,80]. Considering the lack of convincing data, the current recommendation by the American College of Chest Physicians is against the routine use of vena cava filters for prophylaxis in trauma patients [81]. The data are too limited to make a recommendation either for or against vena cava filters in other patient populations, so these must be decided on a case-by-case basis. Vena cava filters probably should be reserved for patients at risk for VTE with contraindications to anticoagulation, bleeding complications from anticoagulation, or recurrent PE in spite of adequate anticoagulation [2].

7. Supportive therapy

The initial therapy for PE may be started before a definitive diagnosis is established or even before the patient leaves the OR, beginning with supportive therapy aimed at stabilizing the patient and minimizing the effect of the embolic occlusion. Vasopressors should be used with the goal of improving RV function and contracting the systemic vasculature to maintain BP and CPP in the face of a fixed obstruction to blood flow caused by the emboli. Wood [1] suggests that norepinephrine

may be the pressor of choice for the treatment of hypotension in patients with massive PE. The beneficial effect of norepinephrine may be due, first, to its α-1 mediated vasoconstriction, which increases BP and RV CPP, as well as increasing venous return. In addition, β1 stimulation by norepinephrine enhances both RV and LV contractility and CO. Alternatives to norepinephrine include dopamine, epinephrine, and dobutamine [82]. However, dobutamine may cause unwanted peripheral vasodilation via a β2 mechanism, and also may decrease arterial oxygenation by changing the V/Q relationships [82,83]. Combined treatment with dobutamine and norepinephrine may be considered.

Pulmonary vasodilators such as inhaled nitric oxide may be useful in decreasing PA pressures, increasing CO, and improving RV function and pulmonary gas exchange in patients with PE, without significantly decreasing systemic BP [84].

8. Anticoagulant and thrombolytic therapy

The perioperative treatment of documented or suspected PE is complicated by an increased risk of bleeding complications, which usually precludes the immediate use of pharmacologic anticoagulants in surgical patients. Most patients should be managed on a case-by-case basis after discussion with the surgical team. The following therapeutic modalities are available for the management of acute PE.

8.1. Anticoagulation

The treatment of PE with pharmacologic anticoagulation has been supported since 1960, when a significant reduction in both mortality and recurrence was seen with UFH versus no treatment [85]. While not directly thrombolytic, anticoagulants allow the body's intrinsic fibrinolytic system to function unopposed, decreasing the thromboembolic burden [2]. Intravenous (IV) or subcutaneous (SC) UFH, SC LMWH, and SC fondaparinux may be used in the initial treatment of acute, non-massive PE [86-89]. The current recommendation by the American College of Chest Physicians is for the use of SC LMWH rather than IV UFH as the initial treatment of acute, non-massive PE [81]. There are, however, certain situations in which IV UFH is preferred because of its shorter duration of action and quick titratability: acute, massive PE, situations with potential for decreased SC absorption, and in patients in whom thrombolysis is being considered or planned [69,81]. Unfractionated heparin also may be preferred in patients with renal insufficiency or morbid obesity, those are who are very thin, or pregnant. The recommended doses and routes of these medications are shown in Table 6.

8.2. Thrombolysis

Thrombolysis for the initial treatment of PE is somewhat controversial. Few studies have directly compared thrombolysis with IV UFH. While the older literature showed that thrombolysis leads to earlier reversal of RV dysfunction when compared with heparin alone [90], a review in 2006 showed no clear benefit of thrombolytic therapy when compared with heparin in the treatment of acute PE [91]. A large meta-analysis by Wan et al. [92] showed a nonsignificant decrease in mortality and increase in major bleeding in all patients with PE who were treated with thrombolysis, not heparin. When this same meta-analysis focused on just patients with major PE, however, the decrease in mortality to 6.2% with thrombolysis, compared

Table 6 Anticoagulant treatment for acute pulmonary embolism [69,81,89]

IV Unfractionated heparin (UFH)	Bolus: 80 U/kg, or 5,000 U *
	Infusion: 18 U/kg/hr or 1,300 U/hr *
	(adjust to APTT equivalent to 0.3 to 0.7 IU/mL anti-Xa activity)
SC UFH (unmonitored)	Initial bolus: 333 U/kg
	Maintenance: 250 U/kg BID
SC UFH (monitored)	Maintenance: 250 U/kg BID (adjust to APTT equivalent to 0.3 to 0.7 IU/mL anti-Xa activity measured 6 hours after injection)
SC LMWH	Enoxaparin 100 IU/kg BID or 150 IU/kg QD
	Dalteparin 100 IU/kg BID or 200 IU/kg QD
	Tinzaparin 175 IU/kg QD
SC Fondaparinux	< 50 kg: 5 mg QD
	50-100 kg: 7.5 mg QD
	> 100 kg: 10 mg QD
Warfarin	Transition to warfarin therapy when patient taking oral and other medications started.

IV = intravenous, SC = subcutaneous, BID = twice daily, APTT = activated partial thromboplastin time, LMWH = low-molecular-weight heparin, QD = once daily.

* For an average 70 kg adult.

with 12.7% in the heparin group, was statistically significant. Nevertheless, in this subgroup of patients the risk of major bleeding was also increased to 21.9%, compared with 11.9% in the heparin group [92]. The risk of major bleeding cannot be understated. The risk of intracranial hemorrhage associated with thrombolysis is as high as 3% in a large registry compared with 0.3% in patients who were not treated with thrombolysis [5]. The recommendation of the American College of Chest Physicians is against the use of thrombolytics in most patients presenting with PE. Patients who may benefit from thrombolysis are those who present with hemodynamic compromise and are judged not to be at high risk of bleeding [81].

8.3. Vena cava filter

Similar to its role in the prevention of PE, the vena cava filter does have a clearly defined role in the treatment of documented or suspected PE. Vena cava filters should be used in the treatment of PE in patients for whom the risk of bleeding is deemed too high to begin anticoagulation. As with prophylactic placement, initiation of a traditional course of anticoagulation is recommended when the bleeding risk resolves [81].

8.4. Pulmonary embolectomy

Surgical embolectomy for PE was first described by Trendelenburg [93] in 1908; Cooley et al. introduced pulmonary embolectomy with cardiopulmonary bypass in 1961 [94]. The indication for surgical embolectomy remains limited to patients with hemodynamic compromise who have failed thrombolysis or have contraindications to thrombolysis [81]. Since 2000, the mortality associated with pulmonary embolectomy has been cited as 6% to 27% [95-98], representing a significant decline from earlier reports of 30% to 55% mortality [99-102].

Catheter-directed intervention with either suction embolectomy/fragmentation or catheter-directed thrombolysis is a relatively new technique that is effective in treating hemodynamically significant PE after failed systemic thrombolysis or as a first-line therapy in patients with contraindications to systemic thrombolysis [103]. The role of catheter-directed techniques has not been studied directly in postoperative patients, but it is clearly an important technique to consider in a hemodynamically unstable patient who is not a candidate for systemic thrombolysis due to recent major surgery.

9. Sequelae of pulmonary emboli

Despite therapy with heparin, oral anticoagulants, and even thrombolytics and vena cava filters in some cases, acute PE has been associated with a 15.3% to 25.3% three-month mortality [5,104] with up to 25% to 32% mortality in patients presenting with RV failure requiring inotropic support [34,105]. Increased mortality is associated with age > 70 years, congestive heart failure, chronic obstructive pulmonary disease, and higher ASA physical status. Other adverse prognostic factors in patients undergoing noncardiac surgery are hypotension and tachypnea at presentation [106], RV hypokinesis, longer surgical time, recent central venous access, and intraoperative blood transfusion [104].

9.1. Recurrent venous thromboembolism

Several studies, the most recent one published by Pengo et al. in 2004 [107], have found the rate of recurrent VTE to be approximately 2.6% to 6.5% within the first 6 months, and 8% to 8.3% within the first year of an initial embolic event. Patients in Pengo et al.'s series all received warfarin treatment for at least 6 months following the initial embolus. In 2006, Schulman et al. found a 29% recurrence rate during the first 10 years following an initial embolus in patients, all of whom received warfarin anticoagulation following their initial event. The rate of recurrence in their series was higher among men, older patients, and those whose initial event was triggered by a permanent factor, as opposed to a temporary factor such as surgery or trauma. A larger proportion of the recurrences (73%) were in patients with prior PEs rather than in patients with prior DVT only (20%). The recurrence rate was not changed by extending the duration of warfarin prophylaxis from 6 weeks to 6 months [108].

Eighty to 85% of patients with acute PE, especially those who receive adequate anticoagulant therapy, will survive the initial event. These patients are at risk of two sequelae: 1) chronic thromboembolic pulmonary hypertension and 2) postthrombotic syndrome. Both sequelae are due to chronic vascular changes that follow the presence of thrombi or emboli, even in the face of post-event anticoagulation therapy.

10. Conclusion

Pulmonary embolism occurs with some frequency in perioperative patients, and should be included in the differential diagnosis of perioperative hypoxemia, hypotension, tachycardia, or acute reduction in end-tidal CO2. Hemodynamic instability is a major risk factor in perioperative patients with PE. Nevertheless, it is often possible to make at least a presumptive diagnosis of PE, and even to begin effective therapy in the OR or early postoperative period.

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