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Review Article**Venous thromboembolism- Prevention, management and anaesthetic considerations****Safiya Imtiaz Shaikh*** and Deep Sengupta*Department of Anaesthesiology, Karnataka Institute Of Medical Sciences, Hubli – 580022, India****Correspondence Info:**

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E-mail: ssafiya11@yahoo.com**Abstract**

Venous thromboembolism has a high incidence in hospitalised patients. These patients may present for surgery. Type of anaesthesia may be considered, general or regional, based on the therapeutic or prophylactic anticoagulant treatment they are receiving and the type and urgency of surgery. Best informed decision regarding the type of anaesthesia can only be made if the anaesthesiologist is abreast with the latest developments in the management of venous thromboembolism.

Keywords: Deep vein thrombosis, pulmonary embolism, thromboprophylaxis, anaesthetic management

1. Introduction

Venous thromboembolism in the form of deep venous thrombosis or pulmonary embolism is one of the concerns mostly in the post operative period.[1] Anaesthesiologists may find themselves responsible for the diagnosis and management of this sometimes fatal disorder. Further, the ongoing surgical procedure may limit the initial management options. Prompt diagnosis and management, however, may reduce mortality and morbidity.

1.1 Incidence

A high incidence of DVT has been found in patients undergoing surgical procedures. Incidence is about 1.3% of DVT in hospitalised patients (2005 report). Without thromboprophylaxis the incidence of DVT is about 14% in Gynecological surgery, 22% in neurosurgery, 26% in abdominal surgery and 45-60% in patients undergoing hip and knee surgery.[2]

PE occurs in approximately 0.3-1.6% of the general surgical population.[3]-[6] Incidence of PE in Thoracic surgery 1.5%-2% [7][8], Abdominal 0.32%-1.0% [9][10], Laparoscopic 0.06%-0.9% [11][12], Vascular 0.4%-0.7% [13][14], Head and neck 0.4%-0.44% [15][16] Gynecologic 0.3%-4.1% [17] Orthopedic procedures: [18] THA 0.7%-30%, TKA

1.8%-7%, hip fracture repair 4.3%-24%, Neurosurgical 0-4% DVT is 3 times more common than PE.

1.2 Patient Risk Factors

- 1) *Hereditary:* Antithrombin deficiency; Protein C deficiency; Protein S deficiency; Factor V Leiden; Prothrombin gene deficiency
- 2) *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
- 3) *Medications:* Heparins; Hormone replacement therapy; Oral contraceptives; Chemotherapy ; Antipsychotics
- 4) *Surgery* (Includes most open abdominal and thoracic procedures): Fracture (hip or leg); Hip or knee replacement; General anaesthesia (when compared with epidural/spinal for lower abdominal and lower extremity surgery)

Patients with malignancy have increased risks associated with hypercoagulable state caused by

both hormones released from the tumor and certain chemotherapeutic agents. Cancer patients also have reduced mobility, frequent presence of indwelling catheters, as well as possible venous obstruction from tumors.

A recent meta-analysis by Carrier *et al* showed that cancer patients have 30VTE events per 100 patient years compared with 12.8 events per 100 patient years in the general population.[19]

2. Pathophysiology

Rudolph Virchow in 1856 described his now famous triad of risk factors for VTE: venous stasis; endothelial damage; hypercoagulable state.[20]

In the lower extremity DVT may arise in the calf veins or in the proximal veins. In the upper extremity DVT may arise due to indwelling CVC and insertion of permanent pacemakers and internal cardiac defibrillators.

Atrial fibrillation may lead to thrombus formation in the right side of the heart. PE occurs in 50% of patients with proximal DVT[21], while asymptomatic thrombosis of leg veins has been observed in 70% of patients with PE[22].

The Damage to the venous valves leads to the development of post-thrombotic syndrome in 25% patients causing chronic venous congestion.[23]

Changes in pulmonary function and gas exchange

The most common gas exchange abnormalities are hypoxemia and an increased alveolar-arterial oxygen tension gradient. Anatomic dead space increases because breathed gas does not enter gas exchange units of lung. Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries. Other abnormalities include-

- ✓ Increased PVR due to vascular obstruction or platelet secretion of vasoconstricting neurohormonal agents such as serotonin. These produce V/Q mismatch.
- ✓ Impaired gas exchange due to increased alveolar dead space from vascular obstruction, hypoxemia from alveolar hypoventilation relative to perfusion in the non-obstructed lung, right to left shunting and impaired DLCO.
- ✓ Alveolar hyperventilation due to reflex stimulation of irritant receptors.
- ✓ Increased airway resistance due to constriction of airways distal to bronchi.
- ✓ Decreased pulmonary compliance due to lung edema, lung hemorrhage or loss of surfactant.

Changes in the circulatory system

Progressive right heart failure is the usual cause of death from PE. Obstruction to blood flow caused by emboli in the pulmonary vasculature and pulmonary outflow tract leads to an increased RV impedance. It is also increased by:

- a) Pre-existing pulmonary disease
- b) Neural reflexes
- c) Release of pulmonary vasoconstrictors in the circulation e.g. serotonin and platelet activating factor from the emboli, activated complement factors 3 & 5 from the plasma and histamine from mast cells. Because of its structure, RV is much more sensitive to pressure than to volume loads.

However, increased RV load leads to RV dilatation and subsequent leftward shift in the interventricular septum, limiting left ventricular filling. Prolonged increase in RV load and pressure ultimately leads to RVF and cardiac output begins to decrease as LV preload decreases.

Laplace's law, Wall stress =
 $(\text{pressure} \times \text{radius}) / (2 \times \text{wall thickness})^{-1}$

Increased wall stress, coupled with systemic hypotension and decreased coronary perfusion pressure, may precipitate RV ischemia and even infarction.

3. Diagnosis

Clinical features of DVT

Upper extremity thrombosis may present with asymmetry in the supraclavicular fossa or in the circumference of upper arms. A prominent superficial venous pattern may be evident on the anterior chest wall.

Lower extremity DVT may present with :

- ✓ Palpatory discomfort in the lower calf
- ✓ Thigh swelling
- ✓ Marked tenderness in the inguinal area/ femoral vein
- ✓ Difficulty or inability in walking

Clinical features of PE

It presents most frequently with dyspnoea. Syncope, hypotension, cyanosis are suggestive of massive PE. Pleuritic pain, cough, hemoptysis are suggestive of small emboli.

Point score methods are useful for estimating the clinical likelihood of DVT & PE[24]

Low Clinical Likelihood of DVT if Point Score Is Zero or Less; Moderate-Likelihood Score Is 1 to 2; High-Likelihood Score Is 3 or Greater	
Clinical Variable	Score
Active cancer	1
Paralysis, paresis, or recent cast	1
Bedridden for >3 days; major surgery <12 weeks	1
Tenderness along distribution of deep veins	1
Entire leg swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial nonvaricose veins	1
Alternative diagnosis at least as likely as DVT	-2
High Clinical Likelihood of PE if Point Score Exceeds 4	
Clinical Variable	Score
Signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100/min	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

Differential diagnosis:**DVT –**

- Ruptured baker's cyst,
- Cellulitis,
- Post phlebitic syndrome,
- Venous insufficiency

PE –

- Pneumonia
- COPD
- CHF
- Pericarditis
- Pleurisy
- ACS
- Anxiety

Diagnostic modalities of DVT:

- i. Compression/duplex ultrasonography of femoral and popliteal veins has both sensitivity and specificity of 97% in detecting DVT in a symptomatic patient.
- ii. Impedance plethysmography has sensitivity of 96%, 50% and 38% for the diagnosis of acute DVT of the proximal, popliteal and distal veins, respectively.
- iii. Contrast venography remains the gold standard for the diagnosis of DVT.
- iv. Radionuclide ascending venography has sensitivity of 90% and specificity of 92% in detecting DVT in the proximal leg veins.
- v. A negative D-dimer result can exclude DVT and PE in a patient with suspected VTE[25][26]

Diagnostic modalities of PE:

- ECG - Geibel *et al* found sinus tachycardia and atrial arrhythmias in 83% patients with a confirmed diagnosis of PE. Non specific ST changes, ST elevation and depression or T wave inversion in ~50% patients.

Other findings seen are Right axis deviation, complete or incomplete RBBB, S₁Q_{III}T_{III} pattern, P pulmonale.

ABG – usual changes found in spontaneously breathing patients are hypoxemia, respiratory alkalosis, hypocapnoea. PaO₂ ≤ 80 mmHg may be present in 26% patients.[27][28] Physiologic dead space – 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.[29] It is calculated using Bohr equation :

$$V_{DPhys} = V_T[(PaCO_2 - PeCO_2)/PaCO_2]$$

X-ray chest – atelectasis or pulmonary parenchymal abnormality may occur in 68% patients. An elevated hemidiaphragm, pleural effusion or pulmonary edema may be present.[30]

V/Q scan – interpretation of V/Q scan using[31]-[36] PIOPED criteria showed high results probability in 87% patients. A normal VQ scan can essentially exclude PE.

Pulmonary angiography is gold standard to detect PE. CT/MRI/spiral CT angiography – high specificity for the identification of main and lobar emboli and can exclude other pulmonary diseases.

Laboratory studies –

- ✓ D-dimer and ELISA are sensitive (96-98%) but very non specific
- ✓ Serum troponinI and troponin T are elevated in less than 50% patients with an acute, moderate to large PE
- ✓ The levels of BNP may be elevated in PE, likely caused by RV dilatation.

Echocardiographic findings associated with PE –

- ✓ RV/LV end diastolic diameter ratio >0.7
- ✓ RV/LV area ratio >0.66
- ✓ RV end diastolic diameter >27mm
- ✓ McConnell sign
- ✓ Septal shift
- ✓ Tricuspid regurgitation >270cm/sec[37]

4. Prophylaxis of VTE

4.1 Pharmacologic: 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 LMWH, low dose unfractionated heparin or fondaparinux.

Unfractionated heparin – For moderate-risk patients, UFH subcutaneous (s.c.) 5000 IU bid; and for high-risk patients, s.c. 5000 IU tid or 7500 IU bid, with the first dose given 2 hours preoperatively. APTT >1.5 times the control value provides adequate thromboprophylaxis.

Low-molecular weight heparins – drugs of choice for thromboprophylaxis. Their therapeutic effect is seen within 2 hours and peak plasma levels within 4 hours.

Prophylactic regimens of LMWH are –

- Prophylaxis started 12 hours before surgery (followed in European countries).
- Prophylaxis started 12-24 hours after surgery (followed in North America).
- Prophylaxis is started more than 12 hours before or 12 hours after surgery (followed by physicians who do not follow above regimens).

Since LMWH is cleared by the kidney, it is recommended that UFH be used instead of LMWH in patients with creatinine clearance <300ml/min.

Fondaparinux – It binds anti-thrombin III, increases its activity and inhibits Factor X_a but has no direct effect against thrombin. Rapidly absorbed, has near 100% bioavailability and a half life of 15 hours that renders it for once daily dosing.[38]

Vitamin K antagonist- Warfarin sulfate or nicoumalone (acitrom) is started on the day of surgery, either preoperatively; or postoperatively in the evening. It is monitored by prothrombin time (PT) (target INR, 2.5; range, 2-3).

Antiplatelet drugs (Aspirin)[39] - it should be used as an adjunct to either UFH or LMWH.

4.2 Mechanical: It is generally efficacious than pharmacologic means of prophylaxis.[40]It reduces the incidence of VTE by as much as 60%when compared with no prophylaxis.[41] It is a method of choice in patients with high risk of bleeding.

- a. Vena caval filters – some studies suggest that filters reduced the incidence of PE[42], no reduction in mortality has been shown and presence of vena caval filters increase the risk of recurrent DVT by as much as 9%[43][44].
- b. Early ambulation should be encouraged in the post-operative period.
- c. Graduated compression stockings apply pressure of varying degree to the leg and thigh, pressure being greatest at the ankle and decreasing proximally. The pressure gradient is able to prevent stasis.
- d. Intermittent pneumatic compression is applied to the legs. These cuffs inflate and deflate alternately to prevent venous stasis.
- e. Mechanical foot pumps help in intermittent plantar compression (IPC) in each foot and augment blood flow in the leg veins.

5. Anaesthetic management

5.1 Preoperative preparation

- i. History of associated co-morbid conditions, with special reference to the risk factors should be noted.

- ii. A thorough physical examination is mandatory.
- iii. Details of anticoagulant drugs-name, type, dosage, duration of treatment, timing of the last dose and duration of discontinuation of the drug-should be noted.
- iv. Risk/ benefit of discontinuation of anticoagulants should be explained to the patient.
- v. An informed consent stating the risks involved in the perioperative period should be taken.
- vi. Investigations – 1. Bleeding time, platelet count, PT and APTT may be performed on the day of surgery. 2. Assessment of anti-Xa level3. Thromboelastography

5.2 Intra-operative management :

Monitoring –

- Pulse, Non-invasive blood pressure (NIBP), SpO₂, EtCO₂, ECG and ST analysis
- In high-risk patients, Central venous pressure (CVP) and arterial BP may be considered.
- ABG analysis and transoesophageal echocardiography may be helpful in suspected cases of PE.

Type of anaesthesia – the decision is to be made based on the type of surgery, urgency of surgery and degree of anticoagulation.

General anaesthesia features significant in a case of VTE –

- There is a hypercoagulable and hypofibrinolytic state post operatively in patients receiving general anaesthesia.[45][45]
- It has been demonstrated by increased levels of thrombin-anti thrombin complexes and fibrinopeptide A
- Surgical factors which promote VTE are the type and duration of procedure.
- Other factors favouring VTE are immobility, concurrent infections, drugs, hypothermia, acidosis, colloids etc.

Regional anaesthesia.[47][47]

The American Society of Regional Anaesthesia guidelines on regional anaesthesia in patients on various anticoagulant agents may be followed if regional anaesthesia is planned.

Heparin –

- Epidural needle/catheter placement/removal may be performed 2 to 4 hours after the last heparin dose if APTT is <1.5 times the normal value.
- Heparin administration should be delayed for 1 hour after the placement of epidural needle or catheter.

LMWH –

- Epidural needle/catheter placement/removal may be performed 10 to 12 hours after the last

thromboprophylactic dose and 24 hours after the last therapeutic dose of LMWH.

- Avoid neuraxial techniques if patient has received LMWH dose 2 hours preoperatively as this coincides with peak anticoagulant activity.

Vitamin K antagonist –

- Discontinue VKA 4-5 days before neuraxial block (INR should be <1.2)[49][49]
- In high-risk patients, “no anticoagulation period” should be kept as short as possible. After discontinuation of these drugs, a highrisk patient may be switched over to heparin or LMWH.

Thrombolytic drugs - Avoid central neuraxial block after thrombolytic therapy with streptokinase, urokinase and recombinant tissue plasminogen activator.

Direct thrombin inhibitors or anti-Xa drugs

- Fondaparinux (Arixtra) — avoid central neuraxial block.
- Melagatran, Ximelagatran — should be stopped 12 hours before surgery.

Antiplatelet drugs –

- Low-dose aspirin (up to 75 mg) does not pose an added risk when performing a neuraxial block and can be continued till the day of surgery.
- Discontinue clopidogrel for 7 days and ticlopidine for 14 days before neuraxial block.
- Epidural needle/catheter placement/removal can be performed 1 to 2 days after the last dose of platelet GP IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban).

5.3 Post-operative management

Monitoring for signs and symptoms of spinal cord compression as a result of spinal cord hematoma. Decompression laminectomy should be performed as soon as the diagnosis is confirmed, preferably within 8 hours. It is advisable to restart the anti-coagulants after surgery.

6. Emerging methods of DVT prophylaxis

An ideal anticoagulant should be easy to administer (preferably oral), should be effective and safe with minimal possible complications or adverse effects, has a rapid onset, has a therapeutic half-life, and requires minimal or no monitoring. The action of the anticoagulant should be predictable with few drug or dietary interactions, and it should be reversible. The drug should also be inexpensive.

1. Tissue factor pathway inhibitors (TFPIs) and nematode anticoagulant peptide (NAPc2). These drugs act through inhibition of the factor VIIa/tissue factor complex.

2. Hirudin was isolated from leech salivary gland tissue. The new drugs include bivalirudin (Angiomax) and lepirudin.

3. Argatroban, which is a carboxylic acid derivative that has been approved for use in the treatment of HIT.

4. Ximelagatran (Exanta; AstraZeneca), a direct thrombin inhibitor consisting of an oral prodrug of melagatran, was first reported in 2003. This agent is rapidly absorbed through the GI tract, where it is converted to its active form, melagatran. It does not require monitoring, as it has a rapid onset of action, a predictable dose-response, and a therapeutic half-life. Also, like the other direct thrombin inhibitors, it does not affect the aPTT or PT.

5. Dabigatran (Pradaxa) is a thrombin inhibitor. It is not approved in the United States for prophylaxis of VTE following hip or knee arthroplasty, but is approved in other countries (eg, Canada).

7. Conclusion

The most effective treatment protocol for a patient with VTE must be determined taking into account for the risk benefit ratio in each situation. Correct diagnosis and prompt management of thromboembolic events in the perioperative period reduces mortality in such patients. Anaesthesiologists must update their knowledge regarding the drugs and methods used in the prevention and management of VTE.

References

- [1] Anaya D. A. and Nathens A. B., “Thrombosis and Coagulation: Deep Vein Thrombosis and Pulmonary Embolism Prophylaxis,” *The Surgical Clinics of North America*, 2005; 85(6): 1163-1177. doi:10.1016/j.suc.2005.10.015
- [2] Stein PD, Beemath A, Olson RE. Trends in the incidence of pulmonary embolism and deep venous thrombosis in hospitalized patients. *Am J Cardiol* 2005; 95:1525-6.
- [3] Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest* 2001; 119(1 suppl):132S-75S
- [4] Geerts WH, Bergqvist D, Pineo GF, et al. American College of Chest Physicians Evidence based clinical practice guidelines (8th Edition). *Chest* 2008; 133(6 suppl):381S-453S.
- [5] Goldhaber SZ, Visani L, De Rosa M. Acute Pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999; 353(9162):1386-9.

- [6] Qadan M, Tyson M, Mcfferty MH, Hohmann SF, Polk HC Jr. Venous thromboembolism in elective operations: balancing the choices. *Surgery* 2008; 144:654-60.
- [7] Nagahiro I, Andou A, Aoe M, Sano Y, Date H, Shimizu N. Intermittent pneumatic compression is effective in preventing symptomatic pulmonary embolism after thoracic surgery. *Surg Today* 2004; 34:6-10.
- [8] Sugarbaker DJ, Jaklitsch MT, Beuno R, et al. Prevention, early detection, and management of complications after 328 consecutive extrapleural pneumonectomies. *J Thorac Cardiovasc Surg* 2004; 128:138-46.
- [9] Sakon M, Kakkar AK, Ikeda M, et al. Current status of pulmonary embolism in general surgery in Japan. *Surg Today* 2004; 34:805-10.
- [10] Rasmussen MS, Jorgensen LN. Postoperative fatal pulmonary embolism in a general surgical department. *Am J Surg* 1995; 169:214-6.
- [11] Sakon M, Kakkar AK, Ikeda M, et al. Current status of pulmonary embolism in general surgery in Japan. *Surg Today* 2004; 34:805-11.
- [12] Inderbitzin DT, Opitz I, Giger U, Kocher T, Krahenbuhl L. Incidence of clinical pulmonary embolism after laparoscopic surgery. *Br J Surg* 2007; 94:599-603.
- [13] Satiani B, Kuhns M, Evans WE. Deep venous thrombosis following operations upon the abdominal aorta. *Surg Gynecol Obstet* 1980; 151:241-5.
- [14] Bani-Hani M, Titi M, Al-Khaffaf H. Deep venous thrombosis after arterial surgery: a literature review. *Eur J Vasc Endovasc Surg* 2008; 36:565-73.
- [15] Moreano EH, Hutchison JL, McCulloch TM, Graham SM, Funk GF, Hoffman HT. Incidence of deep venous thrombosis and pulmonary embolism in otolaryngology-head and neck surgery. *Otolaryngol Head Neck Surg* 1998; 118:777-84.
- [16] Chen C, Disa J, Cordeiro P, Pusic AL, McCarthy CM, Mehrara BJ. The incidence of venous thromboembolism after oncologic head and neck reconstruction. *Ann Plast Surg* 2008; 60:476-9.
- [17] Martino MA, Borges E, Williamson E, et al. Pulmonary embolism after major abdominal surgery in gynecologic oncology. *Obstet Gynecol* 2006; 107:666-71.
- [18] Geerts WH, Bergqvist D, Pineo GF, et al. American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(6 Suppl):381S-453S.
- [19] Elliott CG. Pulmonary physiology during pulmonary embolism. *Chest* 1992; 101(4 Suppl):163S-71S.
- [20] Marcus JT, Gan CT, Zwanenburg JJ. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. *J Am Coll Cardiol* 2008; 51:750-7.
- [21] Goldhaber SZ. Deep venous thrombosis and pulmonary embolism. In: Braunwald E, Kasper DL, Hauser SL, Jameson JL, LoscalFanci AS, editors. *Harrison's Principles of Internal Medicine*, 17th edn. New York: McGraw Hill; 2008. p. 1651-7.
- [22] Virchow R. *Gesammelte Abhandlungen zur wissenschaftlichen Medizin*. Frankfurt a Main, Germany: Medinger Sohn and Co.; 1856. p. 219-732.
- [23] Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; 125:1-7.
- [24] Goldhaber SZ. Deep venous thrombosis and pulmonary embolism. In: Braunwald E, Kasper DL, Hauser SL, Jameson JL, LoscalFanci AS, editors. *Harrison's Principles of Internal Medicine*, 17th edn. New York: McGraw Hill; 2008. p. 1651-7.
- [25] Bombeli T, Spahn DR. Updates in perioperative coagulation: physiology and management of thromboembolism and haemorrhage. *Br J Anaesth* 2004; 93:275-87.
- [26] Deep vein thrombosis and pulmonary embolism. 4th ed. *Anaesthesia and co-existing disease*. In: Stoelting RK, Dierdorf SF editors. Philadelphia: Churchill Livingstone; 2003. p. 169-76.
- [27] Weinmann EE, Salzman EW. Deep vein thrombosis. *N Engl J Med* 1994; 331:1630-42.
- [28] Adess M, Eisner R, Nand S, Godwin J, Messmore HL Jr, Wehrmacher WH. Thromboembolism in cancer patients: Pathogenesis and treatment. *Clin Appl Thromb Hemost* 2006; 12:254-66.
- [29] Lindberg F, Bergqvist D, Rasmussen I. Incidence of thromboembolic complications after laparoscopic cholecystectomy: review of the literature. *Surg Laparosc Endosc* 1997; 7:324-31.
- [30] Gargiulo NJ 3rd, Veith FJ, Lipsitz EC, et al. The incidence of pulmonary embolism in open versus laparoscopic gastric bypass. *Ann Vasc Surg* 2007; 21:556-9.

- [31] Prisco D, De Gaudio AR, Carla R, *et al.* Videolaparoscopic cholecystectomy induces a hemostasis activation of lower grade than does open surgery. *SurgEndosc* 2000; 14:170-4.
- [32] Auer RC, Schulman AR, Tuorto S, *et al.* Use of helical CT is associated with an increased incidence of postoperative pulmonary emboli in cancer patients with no change in the number of fatal pulmonary emboli. *J Am CollSurg* 2009; 208:871-80.
- [33] Elliott CG. Pulmonary physiology during pulmonary embolism. *Chest* 1992; 101(4 Suppl):163S-71S.
- [34] Marcus JT, Gan CT, Zwanenburg JJ. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. *J Am CollCardiol* 2008; 51:750-7.
- [35] Goldhaber SZ. Deep venous thrombosis and pulmonary embolism. In: Braunwald E, Kasper DL, Hauser SL, Jameson JL, LoscalFanci AS, editors. *Harrison's Principles of Internal Medicine*, 17thedn. New York: McGraw Hill; 2008. p. 1651-7.
- [36] Carrier M, Le Gal G, Wells PS, Fergusson D, Ramsay T, Rodger MA. Systematic review: the Trousseau Syndrome revisited: should we screen extensively for cancer patients with venous thromboembolism *Ann Intern Med* 2008; 149:323-33.
- [37] Auer RC, Schulman AR, Tuorto S, *et al.* Use of helical CT is associated with an increased incidence of postoperative pulmonary emboli in cancer patients with no change in the number of fatal pulmonary emboli. *J Am CollSurg* 2009; 208:871-80.
- [38] Elliott CG. Pulmonary physiology during pulmonary embolism. *Chest* 1992; 101(4 Suppl):163S-71S.
- [39] Collaborative overview of randomized trials of antiplatelet therapy – III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994; 308:235-46.
- [40] Marcus JT, Gan CT, Zwanenburg JJ. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. *J Am CollCardiol* 2008; 51:750-7.
- [41] Goldhaber SZ. Deep venous thrombosis and pulmonary embolism. In: Braunwald E, Kasper DL, Hauser SL, Jameson JL, LoscalFanci AS, editors. *Harrison's Principles of Internal Medicine*, 17th edn. New York: McGraw Hill; 2008. p. 1651-7.
- [42] Carrier M, Le Gal G, Wells PS, Fergusson D, Ramsay T, Rodger MA. Systematic review: the Trousseau Syndrome revisited: should we screen extensively for cancer patients with venous thromboembolism? *Ann Intern Med* 2008; 149:323-33.
- [43] Verso M, Agnelli G. Venous thromboembolism associated with longterm use of central venous catheters in cancer patients. *J ClinOncol* 2003; 21:3665-75.
- [44] Goldhaber SZ, Grodstein F, Stampfer MJ, *et al.* A prospective study of risk factors for pulmonary embolism in women. *JAMA* 1997; 277:642-5.
- [45] Van Beek EJ, Kuyper PM, Schenk BE, Brandjes DP, ten Cate JW, Büller HR. A normal lung scan in patients with clinically suspected pulmonary embolism. Frequency and clinical validity. *Chest* 1995; 108:170-3.
- [46] Hatipoglu ON, Hanci E, Tabakoglu E, Altıay G, Cermik TF, Caglar T. A new clinical model in pulmonary embolism and its correlation with V/P scan results. *ClinApplThrombHemost* 2006; 12:344-51.
- [47] Stein PD, Hull RD, Saltzman HA, Pineo G. Strategy for diagnosis of patients with suspected acute pulmonary embolism. *Chest* 1993; 103:1553-9.
- [48] Huisman MV, Büller HR, ten Cate JW, van Royen EA, Vreeken J, Kersten MJ, *et al.* Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. *Chest* 1989; 95:498-502.
- [49] Girard P, Musset D, Parent F, Maitre S, Phlippoteau C, Simonneau G. High prevalence of detectable deep venous thrombosis in patients with acute pulmonary embolism. *Chest* 1999; 116:903-8.
- [50] Garcia D, Ageno W, Libby E. Update on the diagnosis and management of pulmonary embolism. *Br J Haematol* 2005; 131:301-12.