Consensus Statement on Chronic Thromboembolic Disease, Prophylaxis and Special Situations / Abridged Version

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Index

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Abbreviations

CTA	Computed tomography angiography
ANMAT	National Administration of Medicines, Food and Technology
CTEPH	Chronic thromboembolic pulmonary hypertension
CVI	Chronic venous insufficiency
CVP	Central venous pressure
DVT	Deep vein thrombosis
ECMO	Extracorporeal membrane oxygenation
EMA	European Medicines Agency
FDA	Food and Drug Administration
INR	International normalized ratio
LL	Lower limbs
LMWH	Low molecular weight heparin
LCOS	Low cardiac output syndrome
MAP	Mean arterial pressure
MVA	Mechanical ventilatory assistance
NOACs	New oral anticoagulants
NYHA	New York Heart Association
PaO2/FiO2	Ratio of arterial oxygen partial pressure to fraction of inspired oxygen
PAP	Pulmonary arterial pressure
PE	Pulmonary embolism
PEEP	Positive end-expiratory pressure
PH	Pulmonary hypertension
PTE	Pulmonary thromboendarterectomy
PTS	Post-thrombotic syndrome
PVR	Pulmonary vascular resistance
RV	Right ventricle
SBP	Systolic blood pressure
UF	Unfractionated heparin
VKA	Vitamin K antagonists
V/Q	Ventilation/perfusion
VTD	Venous thrombotic disease

1. INTRODUCTION

Chronic thromboembolic disease refers to a set of conditions that manifest over time after acute pulmonary embolism (PE). In most cases, this episode is associated with acute deep vein thrombosis (DVT).

These conditions include chronic pulmonary thromboembolic hypertension (CTEPH), post-thrombotic syndrome (PTS) and chronic venous insufficiency (CVI). (1)

A timely diagnosis and treatment may modify the prognosis of this entity during the course of its free progression. (2)

Damage caused by DVT may lead to valve dysfunction in the deep venous system. (3)

Both CTEPH, PTS and CVI are associated with gradual impairment in the quality of life of those affected. Hence, it is important to postulate prophylaxis strategies in a patient at risk of suffering from a DVT-PE event.

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2. PROPHYLAXIS OF VENOUS THROMBOTIC DISEASE OR DEEP VEIN THROMBOSIS

PROPHYLAXIS IN HOSPITALIZED PATIENTS

The preventive measures for venous thrombotic disease (VTD) are effective and may significantly reduce its occurrence, avoiding up to 80% of thromboembolic events. (1-3)

The variables to be considered are: patient intrinsic thrombotic risk, hemorrhagic risk and clinical scenario or type of surgery.

Prophylactic methods may be divided into mechanical and pharmacological. Scenarios may be clinical or surgical and their possibilities of thromboembolic event risk are low, intermediate and high

CLINICAL SCENARIOS

Patient in critical care unit

This group of patients has a considerable thrombotic risk requiring VTD prophylaxis when there is no contraindication

Non-critical clinical patients

This is a miscellaneous group of patients. The Padua prediction score (4) is useful to assess patients probability of suffering from VTD. It divides patients into two groups: high risk (11.8%) and low risk (0.3%) patients (Table 1).

SURGICAL SCENARIO

In this type of patients, in addition to intrinsic thrombotic risk, surgical thrombotic risk should be considered. Low risk surgeries are ambulatory or with early discharge, and "minor" abdomino-pelvic interventions such as laparoscopy, cholecystectomy, appendectomy, etc. Moderate risk surgeries are intra-abdominal or pelvic surgeries, thoracic and intracranial surgeries when patients are under 40 years of age, since over that age patients are considered to be at higher thrombotic risk. High thrombotic risk surgeries are complex spinal or spinal cord injury surgeries and major osteoarticular surgeries, such as total hip replacement, knee surgery or hip fracture surgery, and those related with cancer in the abdominopelvic cavity.

For high-risk surgeries there is no doubt about the need for prophylaxis, since, according to some series, they have an incidence of VTD close to 50% without preventive methods. Different risk scores may be used for low- and moderate-risk surgeries. The Caprini score (5) is one of the most used (Table 2).

PROPHYLAXIS METHODS

Mechanical

They were mainly studied in surgical patients since drug therapy may increase the risk of bleeding. There are few studies in clinical patients with risk of bleeding and as a complementary approach to drug therapy in patients with higher risk of VTD.

Intermittent pneumatic compression

The effect achieved with this device is to promote circulation, substituting the pump function performed by the muscles of the exercising lower limb. This causes a reduction of blood stasis in bed-ridden patients.

These devices have not shown a reduction in PE mortality, but their beneficial incidence on DVT has been confirmed. Studies in patients undergoing trauma surgery showed that the addition of mechanical prophylaxis to drugs reduced the incidence of DVT by 70%. (6)

Graduated compression stockings

They produce a reduction in the caliber of the vessels with consequent blood flow increase and lower blood stasis. The length of the stockings should be suitable to the patient's height. The use of too long stockings, folded under the knee, may favor venous stasis.

Pharmacological

Heparins

The most commonly used in our country is subcutaneous unfractionated heparin (UFH) at doses of 10,000-(15,000) IU per day, distributed every 8 or 12 hours. It may be used in patients with advanced renal failure and the preventive effect is similar to low molecular weight heparin (LMWH). Up to 15,000 IU/day may be used in patients with increased thrombotic risk.

Table 1. Padua prediction score. Risk of venous thromboembolic disease in non-surgical patients

Risk factor	Score
Cancer	3
Previous thromboembolic disease	3
Expected mobility restricition >3 days	3
Prothrombotic disorder	3
Trauma or recent surgery <1 month	2
Age >70 years	1
Heart or respiratory failure	1
Acute myocardial infarction or stroke	1
Acute infection or rheumatic disorder	1
Obesity (body mass index ≥30)	1
Concomitant hormonal treatment	1
Risk	**Risk of venous thromboembolic disease (%)**
High ≥4 points	11.8
Low <4 points	0.3

Table 2. Caprini's risk score. Risk of venous thromboembolic disease in surgical patients

Risk factor	Score
Age >41 and ≤60 years	1
Minor surgery	1
Lower limb edema	1
Varicose disease	1
Pregnancy or puerperium	1
Spontaneous or repeated abortions	1
Contraception or hormonal therapy	1
Sepsis (last month)	1
Severe pulmonary disease (including pneumonia <1 month)	1
Decreased lung capacity	1
Acute myocardial infarction	1
Heart failure (<1 month))	1
Inflammatory bowel disease	1
Restricted mobility (bed rest)	1
Age ≥61 and <75 years	2
Arthroscopic surgery	2
Open surgery >45 minutes	2
Laparoscopic surgery >45 minutes	2
Malignant neoplasm	2
Bed confinement >72h	2
Plaster cast immobilization	2
Central venous access	2
Age ≥75 years	3
Previous VTD	3
Family member with VTD	3
Factor V Leiden	3
Prothrombin 20210A	3
Lupus anticoagulant	3
Anti-cardiolipin antibodies	3
Hyperhomocysteinemia	3
Heparin-induced thrombocytopenia	3
Other thrombophilia	3
Stroke (last month)	4
Joint surgery	4
Hip, pelvis, or lower limb fracture	4
Acute spinal cord injury (<1 month)	4
Risk	**Score**
Very low	0
Low	1-2
Moderate	3-4
High	≥5

VTD: Venous thrombotic disease. BMI: Body-mass index.

The disadvantages of its use are the mode of administration and the risk of thrombocytopenia (0.7% incidence).

Low molecular weight heparins (LMWH) are more practical due to their possibility of administration every 24 hours. They have a lower incidence of thrombocytopenia (0.3%) with a slight reduction in the incidence of DVT reported in some studies in patients at higher risk. In patients with advanced renal failure (clearance <30 ml/min) the dose should be adjusted. (7)

Pentasaccharides - Fondaparinux

They have the advantage of single daily dose administration without producing thrombocytopenia. According to some studies carried out in patients with increased thrombotic risk (as trauma surgeries), a reduction in the incidence of VTD was observed at the expense of higher bleeding rate. It should not be used in patients with advanced renal failure (clearance<30 ml/min). (3)

Oral Anticoagulants

Vitamin K antagonists (VKA) have limited use in VTD prophylaxis and have also been shown to have a lower effect than LMWH in patients with high thrombotic risk.

New oral anticoagulants (NOACs) are especially useful drugs when extended prophylaxis is required after hospital discharge since, as they use fixed doses that need no further controls, they facilitate adherence. Both rivaroxaban, apixaban, dabigatran and edoxaban have shown similar results, and so any of them may be used. (8-11)

RECOMMENDATIONS

- Preventive measures in addition to early ambulation are not recommended in hospitalized non-surgical patients, low risk surgery and low risk scores (*Class I, Level of evidence B*).
- Pharmacological prophylaxis with LMWH, UFH or fondaparinux is recommended in hospitalized non-surgical patients at high thrombotic risk (*Class I, Level of evidence B*).
- Pharmacological prophylaxis with LMWH or UFH is recommended in critical patients (*Class I, Level of evidence B*).
- Pharmacological prophylaxis with LMWH or UFH (*Class II, Level of evidence B*), or mechanical prophylaxis (*Class II, Level of evidence C*) is recommended in surgical patients at moderate intrinsic risk or by surgical score.
- Pharmacological prophylaxis with LMWH or UFH (*Class I, Level of evidence B*) or fondaparinux. (*Class II, Level of evidence C*) is recommended in surgical patients at high risk. If possible, it is recommended to add mechanical prophylaxis measures (*Class II, Level of evidence C*).
- Use of mechanical rather than pharmacological methods (*Class II, Level of evidence C*) is recommended in hospitalized non-surgical or surgical patients who have indication of prophylaxis and also present high hemorrhagic risk or active relevant bleeding. Once the hemorrhagic risk is solved, onset of pharmacological prophylaxis is recommended (*Class II, Level of evidence B*).
- Pharmacological prophylaxis is recommended in patients undergoing cardiac surgery (*Class II, Level of evidence C*), and in cases where it may not be indicated due to active bleeding or severe thrombocytopenia, mechanical methods should be used (*Class II, Level of evidence C*).
- Extended prophylaxis during 4-5 weeks is recommended in surgical patients at high thrombotic risk due to malignant neoplastic disease and who are at low hemorrhagic risk (*Class I, Level of evidence B*).
- Extended prophylaxis during 4-5 weeks (*Class IIa, Level of evidence B*), with a minimum of 10-14 days (*Class Ia, Level of evidence B*) is recommended in surgical patients with high thrombotic risk due to major trauma surgery.
- NOACs such as apixaban, rivaroxaban, dabigatran or edoxaban may be used as alternative in patients with major trauma surgery (*Class I, Level of evidence B*).

  * Please remember that edoxaban is approved by the FDA but not yet by the ANMAT.

The doses are: apixaban 2.5 mg every 12 hours; rivaroxaban 10 mg once daily; dabigatran 220 mg once daily (150 mg once daily in case of creatinine clearance between 30 and 50 ml/min/1.73m2, age >75 years or concomitant use of amiodarone or verapamil), and edoxaban 30 mg once daily

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3. ANTICOAGULANT TREATMENT OF VENOUS THROMBOTIC DISEASE

The goal of anticoagulant therapy is to prevent thrombus progression and PE, the main complication of DVT.

The standard treatment after an initial stage of anticoagulation with heparin is the use of VKA. At present we have other alternatives such as NOACs either as initial strategy or in cases selected for extended therapy.

In this practical guideline we will try to summarize the indications and alternatives of these therapeutic options as well as the suggested treatment time. (1-2)

RECOMMENDATIONS

- Anticoagulant therapy is recommended for 3 to 6 months in patients with acute DVT provoked by surgery or non-surgical transient risk factor (*Class I, Level of evidence B*).
- Extended anticoagulant therapy is recommended in patients with unprovoked VTD, even if bleeding risk is low or moderate (*Class IIa, Level of evidence B*).
- Extended anticoagulant therapy is recommended in patients with DVT and active cancer, with preference of LMWH over oral anticoagulants (*Class IIa, Level of evidence B*).
- Use of compression elastic stockings is suggested in patients with symptomatic DVT or PTS (*Class IIb, Level of evidence B*).
- Anticoagulant treatment is recommended for 3 months in patients with low risk PE due to surgery or non-surgical transient risk factor (*Class I, Level of evidence B*).
- Extended anticoagulation treatment is recommended in patients with unprovoked PE (*Class II, Level of evidence B*).
- The risk/benefit of continuing anticoagulation should be assessed and, if possible, extended for at least 3 months in patients with unprovoked PE at high risk of bleeding (*Class IIb, Level of evidence C*).
- Direct oral anticoagulants (NOACs) are an alternative to VKA, rivaroxaban, dabigatran and apixaban in low risk PE (*Class I, Level of evidence B*).
- Although there is evidence of its safety and efficacy, certain subpopulations such as cancer, thrombophilia and high-risk PE patients, with or without fibrinolytic therapy or post thrombectomy, have not been adequately represented in clinical trials with NOACs and they should therefore be used with caution (*Class IIb, Level of evidence C*).
- Periodical and routine clinical control with laboratory blood count, renal function and liver enzymes is suggested in the follow-up of patients receiving NOACs (*Class II, Level of evidence B*). (3)

DICOUMARINICS OR VITAMIN K ANTAGONISTS

This treatment will allow continuing long-term anticoagulation. Although prothrombin time is initially prolonged, its anticoagulant effect is obtained after 3 to 5 days and this is why we associate VKA with heparin. Dicoumarinics may be initiated from the first day of treatment and both drugs may be overlapped for 3 to 5 days. Frequent coagulation monitoring is recommended, especially during the initial 3 months, maintaining an INR between 2 and 3. In elderly patients treatment should be initiated at a lower dose than in young adults. In Argentina we have acenocoumarol with a more widespread use and shorter half-life (8 to 12 hours) and warfarin with a longer half-life (36 to 42 hours).

Vitamin K is the natural antidote of these anticoagulants. Its effect starts after 12 hours, so in case of severe bleeding or emergent invasive procedure, prothrombin factor concentrates or fresh frozen plasma should be

used. It should be considered that if doses of vitamin K >10 mg are used; a VKA resistance phenomenon may develop when they are reinitiated, so it is suggested to start with smaller doses and to control their ability to revert daily.

DIRECT ORAL ANTICOAGULANTS (4-11)

They are a valid VKA alternative of anticoagulation. (*Class I, Level of evidence B*) Dabigatran, rivaroxaban, apixaban, and edoxaban are synthetic and specific antagonists against certain coagulation factors (edoxaban is approved by the EMA and the FDA, and is not yet approved in our country). Some of the advantages with these drugs are the prevention of the initial use of heparin (in the case of rivaroxaban and apixaban), no coagulation monitoring requirements, no immune thrombocytopenia generation, a fast action onset of 2 hours, no interference with food and very little interaction with other medicines. Their half-life is short and they have hepatic and renal clearance. In case of severe bleeding they could be reversed with prothrombin concentrates, albeit with scarce clinical experience (12).

The dose of dabigatran in VTD is 150 mg every 12 hours after receiving parenteral anticoagulation for at least 5 to 10 days (*Class I, Level of evidence B*).

Both rivaroxaban and apixaban may be used since the onset of the acute stage and are an alternative to parenteral treatment associated with VKA. However, in such cases, a higher dose should be temporarily used. The initial rivaroxaban dose in VTD is 15 mg every 12 hours for the first 3 weeks and then 20 mg/day on an extended basis. It is not necessary to initially indicate traditional anticoagulation with heparin (*Class I, Level of evidence B*).

The initial apixaban dose is 10 mg every 12 hours during the first week and then 5 mg every 12 hours. Edoxaban is administered at a dose of 60 mg per day or 30 mg per day in the case of creatinine clearance between 30 and 50 ml/min/1.73 m2, weight ≤60 kg and concomitant use of glycoprotein P inhibitors (*Class I, Level of evidence B*).

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4. PULMONARY HYPERTENSION ASSOCIATED WITH CHRONIC THROMBOEMBOLIC DISEASE

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a low prevalence entity, which includes 4% of patients with acute PE. It is a progressive disease of poor prognosis. It is also the only etiology of pulmonary hypertension (PH) with healing potential through pulmonary thromboendarterectomy (PTE). Its diagnosis is initially established by non-invasive studies such as Doppler echocardiography and ventilation/perfusion (V/Q) lung scan.

Confirmatory evaluation and preoperative stratification require a right cardiac catheterization and pulmonary angiography.

EPIDEMIOLOGY

The incidence is difficult to quantify, although in more than 30% of cases there is no history of PE; for this reason, the number of cases is probably larger than estimated. The associated risk factors are history of PE, a major perfusion defect (segmental) in the V/Q scan, idiopathic etiology of PE and younger age. (1)

DEFINITION AND CLASSIFICATION

Chronic thromboembolic pulmonary hypertension integrates group IV of the Nice classification. The diagnosis is established by the presence of PH in patients with thrombi, both chronic and organized in the pulmonary arteries that persist after three months of the acute episode of PE with adequate anticoagulation. Also, CTEPH diagnosis may also be established in patients with no history of PE.

ETHIOPATHOGENESIS

Chronic thromboembolic pulmonary hypertension pathogenesis is multifactorial, and is frequently associated with a DVT/PE event. Despite the evidence relating PE with CTEPH, there are other alternative hypotheses concerning its pathogenesis that suggest primary or secondary arteriopathy to in situ thrombosis as cause of pulmonary vascular occlusion. (2-5)

Different diseases are associated with higher incidence of CTEPH and worse prognosis such as splenectomy, atrial ventricular shunting, infected pacemakers, myeloproliferative disorders, inflammatory bowel disease and chronic osteomyelitis. (6)

CLINICAL PRESENTATION AND DIAGNOSIS

The most frequent symptoms are: intolerance to exercise and dyspnea on exertion. Syncope and hemoptysis are indicators of a significant increase in pulmonary pressures and lead to worse prognosis.

On physical examination, a palpable beat may be found in the second left intercostal space, caused by pulmonary artery dilation due to pressure overload. It is also possible to hear an increase in the intensity of the second heart sound in pulmonary focus and systolic ejection murmur.

Chest X-ray is altered in 90% of cases at the time of diagnosis, with pulmonary artery trunk dilation, increase lobar artery diameters, peripheral oligohemia and cardiac silhouette remodeling with right predominance.

The electrocardiogram has low diagnostic sensitivity, although signs of hypertrophy and right ventricular overload (87%) and right axis deviation (79%) are frequent. (7)

Echocardiography is the technique of choice for screening and early detection of the disease and is useful to rule out other PH causes. It is recommended at 3-6 months after the acute episode in patients with history of PE and then annually for at least the first two years, searching for this complication. The persistence of PH at one year is highly probable with systolic pulmonary pressure >50 mmHg during acute PE. (8)

Ventilation/perfusion scan is the recommended diagnostic study. In CTEPH, a normal or low probability result has a sensitivity of 96% to 99% and a specificity of 94% to 100%.

In case of undefined or inconclusive V/Q scan, a spiral computed tomography angiography (CTA) should be performed.

Multislice computed tomography allows performing an adequate three-dimensional reconstruction and evaluate the pulmonary circulation and anatomy of the right chambers. The greater experience that is acquired with CTA turns it into an option depending on each center.

Selective pulmonary angiography is the gold standard for defining the anatomy and function of the pulmonary tree. It is indicated when there is diagnostic doubt and when planning a surgical strategy.

Right heart catheterization is necessary to define diagnosis, hemodynamic condition and prognosis.

TREATMENT

Pulmonary hypertension due to CTEPH constitutes Group IV in the Nice classification. However, terminal artery disorders of the pulmonary circulation are similar to those found in idiopathic PH. Therefore, both etiologies could respond in a similar way to the specific treatments that proved to be useful in Group I, although there is no evidence to support this statement.

If there is no formal contraindication, PTE is the treatment of choice and the only therapy that offers a healing possibility. (9, 10) The criterion of non-operability must be evaluated by a reference center. (11)

The variables considered to be of poor prognosis are referred to thrombus topography and extension, and to associated comorbidities. (12) In addition, pulmonary vascular resistance (PVR) >1200 dynes.sec.cm-5 is associated with ≥20% mortality.

Indications for pulmonary thromboendarterectomy

- Functional class III-IV (NYHA)
- PVR >300 dynes.sec.cm-5

- Surgical access to thrombi in the main, lobar or subsegmental pulmonary artery.
- Absence of limiting comorbidities.

Postoperative residual PH has been identified as the most important predictor of mortality. (13)

Medical treatment

To date, no drug has been shown to prolong survival in PH.
Medical treatment is indicated in:
1. Patients with CTEPH without surgical or instrumental criteria.
2. Postoperative residual PH therapy

Anticoagulation is indicated with an INR value between 2 and 3. The justification of anticoagulation obeys the prevention of recurrent embolic episodes and in situ thrombosis.
In recent years, several clinical trials with pulmonary vasodilators have been performed in non-surgical CTEPH with some promising results.

Percutaneous pulmonary angioplasty

Initial encouraging results have been published. Inoperable patients could be considered potential candidates for this therapy in centers with experience. (14)

Lung transplantation

It is the last available option when all the others are not possible or have failed.

CONCLUSIONS

Chronic thromboembolic pulmonary hypertension requires a high index of clinical suspicion. Pulmonary V/Q scan plays an essential role in discriminating PH diagnosis. The therapeutic strategy of choice is PTE with curative effects in suitably selected cases.

RECOMMENDATIONS

- Pulmonary V/Q scan is recommended in patients with suspected CTEPH or unexplained PH due to respiratory or left cardiac cause (*Class I, Level of evidence C*).
- Contrast pulmonary CTA with PE protocol is recommended to supplement the information, in the absence of V/Q scan or centers with high experience availability (*Class I, Level of evidence C*).
- Pulmonary angiography should always be performed in patients with CTEPH considering an eventual intervention (*Class IIa, Level of evidence C*).
- Right heart catheterization is indicated to confirm the diagnosis and to decide therapeutic strategies (*Class I, Level of evidence C*).
- Long-term anticoagulation is indicated in all CTEPH patients (*Class I, Level of evidence C*).
- Riociguat is indicated in symptomatic patients with persistent non-surgical CTEPH or with postoperative recurrence (*Class I, Level of evidence B*).
- Use of approved drugs for PH in symptomatic patients not candidates for PTE (*Class IIb, Level of evidence B*).

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5. SURGICAL TREATMENT OF CHRONIC PULMONARY EMBOLISM

PULMONARY ENDARCTERECTOMY

Patients with CTEPH should be thoroughly studied and discussed to evaluate the feasibility of performing pulmonary endarterectomy. Its technical probability should be established according to the location of the thrombi, as well as its pertinence considering comorbidities or the existence of contraindications such as severe left ventricular systolic dysfunction, severe chronic obstructive pulmonary disease and advanced oncological disease. Hemodynamically, the presence of elevated PVR >1,100, 1,200 and 1,300 dynes.sec.cm-5 is a prognostic factor of mortality. (1-3)

Unlike pulmonary embolectomy, in the context of acute PE, this surgical intervention is a true pulmonary endarterectomy; the approach is by bilateral median sternotomy, under general anesthesia and starting by the right pulmonary artery. The technique requires extracorporeal circulation, deep hypothermia (between 17-20ºC) and intermittent circulatory arrest, with 20-minute maximum arrest with reperfusion periods. Circulatory arrest is necessary to control, in different degrees, retrograde blood flow caused by the bronchial circulation (which nourishes the pulmonary parenchyma), thus allowing a correct visibility of the surgical field to identify the correct dissection plane that ensures a complete procedure. Brain protection during circulatory arrest is performed with thiopental sodium, phenytoin and local cold application. One gram of methylprednisolone is administered to prevent or mitigate reperfusion injury after surgery. Hemodilution is performed to decrease blood viscosity, maintaining a hematocrit level between 18% and 25% during deep hypothermia and circulatory arrest. After aortic clamping, antegrade cold cardioplegia solution is administered for myocardial protection. During rewarming, 500 mg of methylprednisolone is administered and the interatrial septum is inspected for the presence of patent foramen ovale. The pulmonary arteries are opened in their intrapericardial area and proximal to distal endarterectomy is performed up to, as closely as possible, the segmental levels, and if possible, the subsegmental levels. (4-6) Short- and long-term survival outcomes are auspicious. (7-9)

Also, in required cases, pulmonary endarterectomy may be combined with other surgical procedures, such as myocardial revascularization surgery, patent foramen ovale closure, pulmonary valve replacement or repair of pulmonary artery aneurysm. Cognitive function is generally not affected and surgery may be performed in elderly patients with an acceptable risk. (10)

On the other hand, morbidity and mortality after surgery depend on the presence of persistent or recurrent PH.(7) Persistent PH is defined as mean pulmonary arterial pressure (PAP) ≥25 mmHg in the last measurement performed in the postoperative intensive care unit.

RECOMMENDATIONS

- Pulmonary endarterectomy is recommended in patients with CTEPH, who present anatomical and functional conditions and no contraindications (*Class I, Level of evidence C*).
- Pulmonary artery angioplasty may be considered in symptomatic patients without indication of pulmonary endarterectomy or inadequate risk/benefit (*Class IIb, Level of evidence C*).

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6. CLINICAL MANAGEMENT OF POSTOPERATIVE PULMONARY THROMBOENDARTERECTOMY IN CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

INTRODUCTION

The postoperative PTE period in CTEPH represents a clinical scenario where different types of shock can coexist, with blood oxygenation and hemostatic disorders representing a great challenge for the clinical cardiologist and the intensivist physician. The most relevant complications are postoperative respiratory insufficiency due to multiple mechanisms and right ventricular failure. (1-3)

NORMAL POSTOPERATIVE PERIOD

Normally, patients in postoperative PTE period will require mechanical ventilatory assistance (MVA) for 48 to 72 h, depending on the institutional protocol. (4) Protective ventilation is recommended with the following initial parameters; tidal volume: 6-8 ml/kg, respiratory frequency: 12-18/min, positive end-expiratory pressure (PEEP): 8-10 cmH2O, maintaining plateau pressure below 30 cmH2O and plateau pressure - PEEP below 16 cmH2O (Table 1)

Preventive maneuvers will be systematically used to avoid reperfusion pulmonary edema, including prevention of fluid overload, maintenance of adequate diuretic rhythm and evaluation of possible negative balance. (5)

Weaning from mechanical ventilation will be performed with pressure support plus PEEP until blood gas levels and adequate tissue perfusion parameters are achieved. Onset of weaning will be postponed in cases of perioperative ischemia, lactic acid >4 mEq/L, bleeding >200 ml/h or perioperative stroke. Afebrile patients with hemodynamic stability with PEEP <6 and ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO2/FiO2) >200 could initiate weaning from MVA. Patients presenting a Tobin index (respiratory frequency/tidal volume) <100 and who do not present failure with the spontaneous respiratory test during 30 min (Table 2), with adequate blood gas levels (pH >7.30, PO2> 60 mmHg, PCO2 <50 mmHg, O2 sat >90%) and with airway protection will be candidates for extubation.

Table 1. Protective ventilation

Tidal volume	6-8 ml/kg
Respiratory frequency	12-18 cycles per min
PEEP	8-10 cmH2O
Plateau pressure	<30 cmH2O
Plateau pressure – PEEP	<16 cmH2O

PEEP: Positive end-expiratory pressure.

Some patients will require noninvasive ventilation during the first postoperative days and a lower percentage will need reintubation due to weaning failure for respiratory or hemodynamic causes.

Patients using nitric oxide due to residual PH or right ventricular failure and who are in planned MVA weaning will have to gradually reduce the dose and eventually incorporate another inhalation or oral agent (iloprost, sildenafil).

Use of a pulmonary artery catheter or echocardiographic follow-up is recommended for hemodynamic monitoring. The most frequent hemodynamic profile after PTE is the significant and early decrease of PAP and increased cardiac output with PVR normalization. On occasions, increased cardiac output is not accompanied by significant PAP and PVR reduction until 24-48 h after surgery. (6)

Adequate right ventricular preload must be ensured without exceeding a central venous pressure (CVP) of

Table 2. Spontaneous respiratory test

Spontaneous respiratory test (initial and 30-min assessment)	
The occurrence of any of the following is considered failure	
Heart rate	>140 or <60 bpm or 20% increase from baseline
Systolic blood pressure	<90 or >180 mmHg
O2 saturation	<90%
Respiratory frequency	>35 cycles per min
Tissue hypoperfusion parameters	Lactic acid >2 mEq/L or central venous O2 saturation <65%
Sensory impairment or mental agitation	
Poor ventilatory mechanics	

15 mmHg to minimize wall stress. In case of suboptimal heart rate, epicardial pacing may be attempted at 90-100 beats per minute. Inotropic and vasopressor support with low dose dobutamine and/or noradrenaline is the usual approach, with hemodynamic objectives destined to reduce reperfusion edema (cardiac index <3 L/min/m2) and maintain a mean arterial pressure (MAP) between 60 and 65 mmHg. In case of hypertension >140/90 mmHg, use of sodium nitroprusside may be necessary.

RESPIRATORY INSUFFICIENCY

Most patients present a phenomenon of pulmonary artery "steal" secondary to the existence of different vascular resistances along the vascular tree, so that pulmonary arterial flow is redistributed to de novo revascularized sectors. (7, 8) This produces hypoxemia due to altered V/Q. Treatment consists in support protective ventilation until tissue perfusion parameters are achieved and weaning criteria are accomplished. Normally, this phenomenon reverses after various weeks or a few months. (9)

REPERFUSION PULMONARY EDEMA

Between 48 and 72 h after surgery, approximately a third of patients may present non-cardiogenic pulmonary edema due to increased capillary permeability, secondary to release of cytokines, inflammation mediators and free radicals. (10) It is probable that the patient is already extubated at the moment this complication appears. Patients present hypoxemia and pulmonary infiltrates generally distal to the reperfused area, in most cases consisting of mild forms. (11, 12)

Patient management is similar to that of distress with protective ventilation with low tidal volume (4-6 ml/kg), plateau pressure <30 cmH2O and plateau pressure - PEEP <16 cmH2O. Alveolar recruitment maneuvers may be used and early prone decubitus position may be considered.

Occasionally, the objective may be reached with PaO2/FiO2 near 200 with PaO2 between 60 to 80 mmHg and O2 saturation between 90% and 95%. After weaning, some patients may require noninvasive ventilation to achieve therapeutic objectives.

Some patients could benefit with the use of inhaled nitric oxide at 10-20 ppm and on occasions at higher doses (up to 60 ppm) or prostaglandins (for example, iloprost) (13-16) In the case of refractory hypoxemia, if pulmonary pressures are acceptable and there is no significant hemorrhage, veno-venous extracorporeal membrane oxygenation (ECMO) is a costly but effective therapeutic option that would avoid the use of elevated airway pressures and deleterious FiO2, and occasionally avoid MVA. In more severe refractory patients due to right ventricular failure or severe residual PH, availability of veno-arterial ECMO might compensate the patient as bridge to recovery or lung transplantation.

RIGHT VENTRICULAR FAILURE

Residual PH is the main cause associated with postoperative development of right ventricular failure. Other associated causes are extracorporeal circulation, hypothermia and inadequate right ventricular protection. These patients are not candidates to initiate weaning from MVA. The therapeutic objective is to maintain MAP between 60-65 mmHg, systolic blood pressure (SBP) >80 mmHg and achieve adequate tissue perfusion with central venous O2 saturation objectives ≥65%, normal lactic acid levels (<2 mEq/L) and diuresis >0.5 ml/kg/h. A CVP not higher than 15 mmHg will be sought as well as minimum inotropic support to keep an adequate MAP, but not above 65 mmHg, or a cardiac index between 2 and 3 L/min/m2. Internal milieu equilibrium should be maintained with adequate blood glucose (<140 mg/dl) and potassium (<4 mEq/L) levels, avoiding acidosis.

(17) Nitric oxide can be useful with doses of 5 to 20 ppm, and eventually higher doses, with gradual reduction until weaning. Occasionally, patients may present low cardiac output syndrome (LCOS) due to left ventricular dysfunction, especially in those with preexistent cardiac disease, associated non-revascularized coronary heart disease, perioperative acute myocardial infarction or post-pump stunning. Hemodynamic management should aim to provide adequate loading pressures of both ventricles with CVP >10 mmHg but <15 mmHg and pulmonary capillary pressure <18 mmHg. Inotropic support will be preferably performed with dobutamine (up to 10 μg/kg/min), or milrinone (up to 0.5 μg/kg/min) and eventually vasopressin (up to 0.04 IU/ min) or noradrenalin (up to 0.5 μg/kg/min). The objective is to achieve an adequate aortic-coronary gradient to avoid myocardial ischemia. Use of systemic vasodilators such as nitroprusside or nitroglycerin may be eventually considered to reduce left ventricular afterload, especially in cases with associated left ventricular failure. Both in patients with right ventricular failure as those with LCOS due to left ventricular failure, who are refractory to treatment with pharmacologic circulatory support, veno-arterial ECMO should be considered. (18-19)

RECOMMENDATIONS

- In its most severe form, MVA is indicated using protective ventilation with low tidal volume (4-6 ml/kg, plateau pressure <30 cmH2O and plateau pressure - PEEP <16 cmH2O (*Class IIa, Level of evidence C*).
- Alveolar recruitment maneuvers may be used, considering early prone decubitus position to avoid oxygen toxicity (*Class IIb, Level of evidence C*).
- Veno-venous ECMO is reserved for refractory hypoxemia and in the absence of significant coagulopathy (*Class IIa, Level of evidence C*).
- An urgent echocardiogram should be performed if right ventricular failure is suspected (*Class I, Level of evidence B*).
- The therapeutic objective is to maintain MAP between 65-70 mmHg, SAP >80 mmHg, diuresis >0.5 ml/kg/h, CVP <15 mmHg and achieve adequate tissue perfusion with central venous saturation ≥70% and normal lactic acid levels (<2 mEq/L) (*Class I, Level of evidence C*).
- Use of minimum inotropic support is suggested to maintain an adequate MAP of 65-70 mmHg or cardiac index between 2 and 3 L/min/m2 (*Class IIa, Level of evidence C*).
- Inotropic support will be preferably performed with dobutamine (up to 10 μg/kg/min,) or milrinone (up to 0.5 μg/kg/min) and eventually with vasopressin (up to 0.04 IU/ min) or noradrenaline (up to 0.5 μg/kg/min) in case of arterial hypotension (*Class IIb, Level of evidence C*).
- In case of difficult to manage right ventricular failure associated with PH, 5 to 20 ppm nitric oxide should be considered (*Class IIa, Level of evidence C*).
- In case of right ventricular or biventricular failure due to LCOS which does not stabilize with maximum circulatory pharmacologic support, veno-arterial ECMO should be considered (*Class IIa, Level of evidence C*).
- In case of arterial hypotension secondary to vasoplegia not responding to 1-2 liter crystalloid expansion, vasopressors (noradrenaline, phenylephrine or vasopressin) should be indicated for clinical and hemodynamic stabilization (*Class IIa, Level of evidence B*).
- Anticoagulation should be started as soon as possible, due to high risk of thromboembolic events (*Class I, Level of evidence B*).
- Non-fractionated sodium heparin by continuous infusion without bolus should be initiated 8-12 h after surgery. This treatment is optional in cases of hemodynamic instability, ventricular assistance, renal failure or high risk of bleeding (*Class I, Level of evidence C*).
- In patients who progress without complications, with low surgical drain discharge and acceptable tissue perfusion parameters, anticoagulation with LMWH could be started (*Class I, Level of evidence C*).

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7. CHRONIC VENOUS THROMBOTIC DISEASE. POST-THROMBOTIC SYNDROME

Post-thrombotic syndrome is a long-term consequence of DVT which may occur despite optimal anticoagulant therapy. The most common signs and symptoms are pain, swelling, edema, heaviness, fatigue, hyperpigmentation and/or subcutaneous fibrosis of the affected limb. More severe manifestations include ulcers and venous claudication. (1, 2)

EPIDEMIOLOGY

The incidence of PTS is still elevated, affecting 1-3‰ of the overall population. Among these patients, 20 and 50% will develop some degree of PTS, and 5 to 10% will present severe complications such as ulcers (3-5)

PATHOPHYSIOLOGY

Post-thrombotic syndrome pathophysiology is complex and has not been clearly elucidated; however, venous hypertension and local inflammatory phenomena would be involved in its development (Figure 1). (6-8)

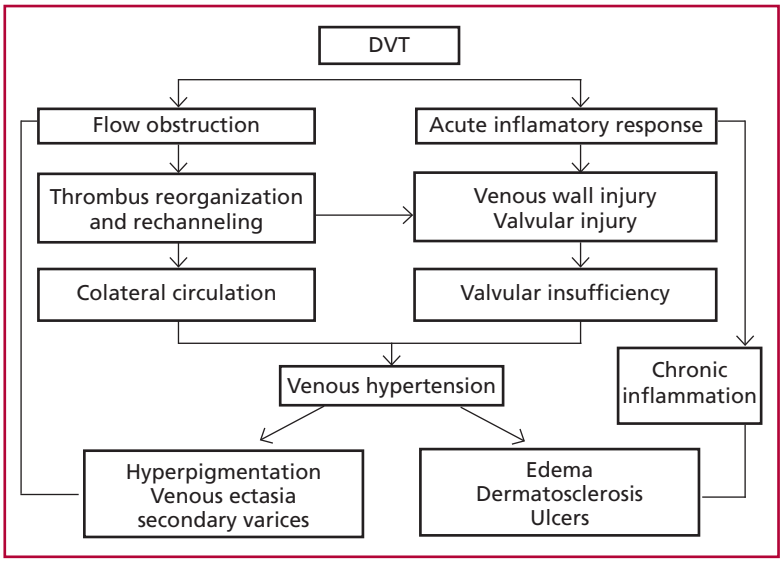

Fig. 1. Pathophysiology of post thrombotic syndrome.

DIAGNOSIS

Diagnosis of post-thrombotic syndrome is essentially clinical, based on characteristic signs and symptoms (Table 1). Since PTS is a chronic entity, which may have a fluctuating course, it is recommended to wait at least 3 to 6 months of acute DVT resolution to consider its presence. (9)
The Villalta score and Ginsberg's definition may be used for its diagnosis and assessment.

The Villalta score

The Villalta score (Table 2) incorporates five subjective and six objective parameters and presence or absence of ulcers. It has good correlation with the patient's quality of life and venous anatomy. (10) It is useful to diagnose and determine PTS severity. A score >5 indicates the presence of PTS, between 5 and 9 mild PTS, from 10 to 14 moderate PTS and >15 or presence of ulcers severe PTS.

Table 1. Clinical characteristics of post-thrombotic syndrome

Symptoms	Signs
Pain	Edema
Heaviness	Varices
Cramps	Ectasia / venous dilation
Fatigue	Cyanosis
Pruritus	Hyperpigmentation
Paresthesia	Eczema
Venous claudication	Lipodermatosclerosis
	Ulcers

Ginsberg definition

Ginsberg defines PTS as the presence of characteristic daily pain and edema (worsens standing or walking and improves with rest and elevated limb), persisting for at least one month and occurring at least 6 months after an episode of DVT. (11, 12)

Table 2. The Villalta score.

	Absence	Mild	Moderate	Severe
Symptoms				
Pain	0 points	1 point	2 points	3 points
Cramps	0 points	1 point	2 points	3 points
Heaviness	0 points	1 point	2 points	3 points
Paresthesia	0 points	1 point	2 points	3 points
Pruritus	0 points	1 point	2 points	3 points
Signs				
Pretibial edema	0 points	1 point	2 points	3 points
Hyperpigmentation	0 points	1 point	2 points	3 points
Venous ectasia	0 points	1 point	2 points	3 points
Erythema	0 points	1 point	2 points	3 points
Dermal Induration	0 points	1 point	2 points	3 points
Pain on calf compression	0 points	1 point	2 points	3 points

RISK FACTORS FOR THE DEVELOPMENT OF POST-THROMBOTIC SYNDROME

Body mass index and age are included among the risk factors for the development of PTS. Iliac or common femoral vein involvement present with greater risk than femoro-popliteal involvement. (7) Recurrent thrombotic events in the index limb, presence of residual thrombosis and sub-optimal treatment are risk conditions for the development of PTS.

PREVENTION OF POST-THROMBOTIC SYNDROME

- Anticoagulant treatment with optimal dose and duration. (13)
- Daily use of class II graded compression stockings, with 30-40 mmHg at the ankle level, for at least 2 years,

except in case of peripheral arteriopathy. (11, 13, 14)
- Early walking.
- Directed catheter thrombolysis in patients with proximal DVT, which would reduce PTS at 24 months compared with standard therapy. (15-17)

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8. PULMONARY EMBOLISM IN SPECIAL SITUATIONS

DIAGNOSIS AND TREATMENT OF THROMBOEMBOLIC DISEASE IN PREGNANCY

Pulmonary embolism is one of the most important causes of maternal mortality during pregnancy. The risk increases in postpartum, especially after a cesarean section.

Signs and symptoms do not differ from those seen in the general population, although it is worth remembering that higher heart rate and low blood pressure are normal characteristics of advanced pregnancy. Dyspnea should be also interpreted with caution, since it is frequent in the last trimester. It is normal for the D-dimer level to increase during pregnancy, but it maintains its negative predictive value in patients with low clinical suspicion. In patients with low-moderate risk, negative high-sensitivity tests rule out PE in 95% of cases, avoiding exposure to more aggressive diagnostic methods.

In patients with clinical suspicion of PE, a negative D-dimer leads to perform imaging studies, beginning with Doppler ultrasound of the lower limbs (LL). If this is positive, the diagnosis of thromboembolic disease is confirmed and anticoagulation with heparin will be initiated. (1)

Other options to obtain a diagnosis if DVT is not demonstrated are Doppler echocardiography, radioisotopic V/Q scan, CTA with PE protocol and pulmonary angiography. Although multislice CTA is currently the method of choice, V/Q scan is preferred in pregnancy for its lower exposure to radiation, especially when chest X-ray is normal and only perfusion may be performed. (2, 3) Another option to avoid irradiation is transthoracic echocardiography, which allows detecting proximal thrombi in the pulmonary arteries, right heart thrombus in-transit, assessing the degree of PH, adequacy of the RV, and ruling out the existence of a permeable foramen ovale. If the examination is negative, a transesophageal echocardiogram, preferably three-dimensional, may be performed, since it is excellent for detecting thrombi in up to second order vessels.

Pulmonary angiography increases ten-fold the exposure to radiation and should be avoided.

Initial treatment is based on the use of heparin in its different variants, as it does not cross the placental barrier. Anticoagulation is continued for at least 3 months including the 6 weeks postpartum. As no studies sup-

port the use of fondaparinux and NOACs, they are formally contraindicated. Vitamin K antagonists may cause fetal malformations or bleeding at any time during pregnancy, and are therefore absolutely contraindicated. In contrast, they may be administered during puerperium and lactation.

Pregnancy is considered a relative contraindication for the use of fibrinolytics. However, they have been used in critical situations, and the evidence available arises from the report of cases with complication rates similar to those of other populations. As in other clinical situations, the patient should be adequately stratified to assess the risk of implementing a more invasive reperfusion strategy.

RECOMMENDATIONS

- Sodium heparin or LMWH is used for treatment (*Class I, Level of evidence C*).
- Dicumarinics are teratogenic and are contraindicated (*Class I, Level of evidence B*)
- NOACs and pentasaccharides have not been tested and should not be used (*Class I, Level of evidence C*).
- Fibrinolytics have been successfully reported in isolated cases. Their use is restricted to severely ill patients (*Class IIb, Level of evidence C*).
- High sensitivity D-dimer has 95% negative predictive value (*Class I, Level of evidence B*).
- Doppler ultrasound (LL, transthoracic, transesophageal) is a valuable diagnostic tool that prevents irradiation in the mother and fetus (*Class IIa, Level of evidence C*).
- For the same reason, perfusion scan is now preferred to multislice computed tomography (*Class I, Level of evidence B*).

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9. DIAGNOSIS AND TREATMENT OF THROMBOEMBOLIC DISEASE ASSOCIATED WITH NEOPLASMS

PROPHYLAXIS

The presence of neoplasia increases the risk of thromboembolic disease between 4 and 16 times. The risk is greater in brain, pancreatic and multiple myeloma tumors followed by lung, kidney, uterus, and bladder tumors. Chemotherapy is an additional risk factor. Surgery may increase VTD risk up to 90 times, so extended prophylaxis is recommended. Although risk decreases over time, it continues to be elevated for one year; therefore, the recommended duration of prophylaxis is 30 days. (1) There is no evidence of improved prognosis in its prolongation. It is recommended to use LMWH over other anticoagulant methods. (2)

DIAGNOSIS

The same diagnostic guidelines used for the general population are followed for these patients, although it should be remembered that D-dimer has more false positives.

TREATMENT

This population should be considered as having a higher risk of bleeding, although treatment is not different from other populations. Therapy is maintained for at least 3 to 6 months in the first episode and LMWH is recommended. When the risk of recurrence is high, anticoagulant treatment will be considered until the resolution of the underlying disease or indefinitely.

SPONTANEOUS PULMONARY EMBOLISM AND OCCULT NEOPLASM

Ten per cent of patients with VTD present or develop cancer in the years after diagnosis. Periodic screening is recommended. Thorough screening has not shown to be superior to basic screening. (3)

RECOMMENDATIONS

- Initial management does not differ from standard management (*Class IIa. Level of evidence B*).
- It is suggested to use LMWH for 3-6 months during follow-up (*Class IIa. Level of evidence B*).

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10. NONTHROMBOTIC PULMONARY EMBOLISM

Nonthrombotic pulmonary embolism refers to the occlusion of the pulmonary tree by different nonthrombotic materials such as fat cells, amniotic fluid, tumor cells, different microorganisms, air or gas.

The prevalence of these forms of embolism is low and the clinical presentation does not differ from thrombotic embolism. For this reason the environment, practices and other clinical conditions that surround the patient in whom an embolism of nonthrombotic etiology is suspected are more relevant. Some of the most common clinical manifestations, as in PE, are: dyspnea, tachycardia, hemoptysis, chest pain and even syncope. (1, 2)

As it is a rare entity, no information from large trials is available.

AMNIOTIC FLUID EMBOLISM

It is a rare entity, with an incidence of 1 to 12 cases per 100,000 deliveries. (3, 4)

The factors most associated with this syndrome are: advanced maternal age, labor instrumentation, premature placental abruption, placenta previa, multiparity, cervix lesions, eclampsia and labor induction. It is an unpredictable condition difficult to prevent. (5)

Fluid embolism occurs when this enters the systemic circulation through the uterine veins during labor, through placental lacerations that may be generated as a result of instrumentation or as a result of traumatic labor.

Epithelial cells and meconium impact at the pulmonary artery level causing their obstruction (pulmonary embolism) and triggering a great inflammatory reaction. Convulsions and respiratory collapse due to pulmonary edema and acute respiratory distress syndrome are common. Mortality oscillates around 20% and the treatment is hemodynamic support. (4, 5)

TUMORAL EMBOLISM

Tumor cells arrive to the systemic circulation through the invasion of capillaries or through the neovasculature generated by the tumor itself. Most of the cells that escape into the bloodstream are captured and lysed by the immune system or by mechanical and vascular shear forces. However, some of them may access the pulmonary circulation and become trapped inside the capillaries. These micro-embolisms often pass clinically unnoticed; according to one study, the post mortem diagnosis in patients with solid tumors is only about 23%. (6)

As additional factor, it is worth mentioning that the presence of tumor cells at the level of the pulmonary vasculature may activate the coagulation cascade with the formation of an occlusive thrombus.

Within the solid forms of cancer, those of the breast and liver appear to be more associated with predominantly tumor type PE, while prostate, stomach and caecal appendix tumors present a double tumor and thrombotic mechanism. Lung cancer could also present either of the two embolic forms. (7)

Changes in the pulmonary vasculature, such as media hypertrophy, intimal fibrosis, and necrosis of the elastic layer may be irreversible and progress towards chronic PH.

Anatomically, there is a difference depending on the type of embolism; intimal proliferation induced by tumor embolism is usually concentric and with high cellular content, whereas thrombotic embolism is “meandering” and with greater eccentricity.

From clinical presentation to simple chest x-ray, pulmonary microembolism resembles other respiratory pathologies such as pneumonia, interstitial lung disease or even tuberculosis. (7)

There is no specific treatment for this entity. Survival may improve in tumors with good response to chemotherapy. In order to arrive to the pre-mortem diagnosis, it is necessary to be attentive to the possibility of presentation and to consider it in a patient with solid neoplasm presenting with respiratory symptoms or compatible with PE. Finally, treatment should be supportive and focused on the underlying disease.

SEPTIC EMBOLISM

Septic PE has a clear association with tricuspid valve endocarditis (right-sided endocarditis). This clinical condition, in turn, is associated with intravenous drug addiction, presence of infected catheters (both permanent and semipermanent) and devices such as permanent pacemakers or implantable cardioverter defibrillators that are

colonized by pathogenic microorganisms. In addition, thrombophlebitis, suppurating processes of the head and neck and vascular prostheses are also possible embolic sources. As for the presentation form, febrile episodes, respiratory symptoms and pulmonary infiltrates are usually the most common initial findings.

In this circumstance, the treatment is based on specific antibiotic therapy. It is a priority to identify the embolic source and the causative microorganism. For this purpose, imaging techniques are useful: ultrasound and computed tomography together with serial cultures of peripheral blood and of all the material with suspected etiology extracted from the body. It should be noted that right endocarditis has a higher incidence of negative blood cultures.

The most common germ is Staphylococcus aureus. However, the incidence of anaerobic, bacterial and fungal microorganisms increases as a result of immunosuppressive states in chronic neoplastic patients.

It is essential to eliminate the septic focus (catheter, pacemaker, prosthesis) and promptly initiate specific antimicrobial treatment. (8, 9)

FAT EMBOLISM

Fat embolism is a rare complication of long bones or pelvis fracture and of surgical procedures such as placement of intramedullary devices, hip or knee prostheses. Use of intraosseous route, polytransfusion of blood products, fatty liver, pancreatitis and liposuction are also described as a complication of external trauma. In the case of fractures, its incidence increases with the higher number of involved bones.

Mortality ranges from 5% to 15% according to the series. (10)

In addition to total or partial occlusion of the pulmonary arterial tree or any of its branches, a local inflammatory reaction is triggered that may evolve to acute respiratory distress. Half of the patients present with respiratory failure needing orotracheal intubation. (11)

The clinical presentation includes an altered mental state that may be accompanied by focal neurological signs resulting from cerebral fat embolism. Another sign is the late appearance (12 to 36 hours) of a cutaneous rash resulting from small dermal capillary embolization. A typical triad of fat embolization is thus described: altered mental state and/or focal neurological signs, respiratory distress and cutaneous-mucosal rash that is mainly located in the conjunctiva, oral mucosa and skin of the neck and armpits.

Preventive treatment with six doses of methylprednisolone at 1.5 mg/kg every 8 hours is described in patients at high risk for fat embolism (fracture of the long bone and/or pelvis). (12) Furthermore, the treatment is supportive.

VENOUS GAS EMBOLISM

The entry of air into the blood vessels usually represents an iatrogenic complication. It usually occurs after manipulation of central venous and dialysis catheters. According to different sources, it is estimated that the volume necessary to generate severe damage or death ranges from 50 to 500 ml. (13)

Air embolism causes increased pulmonary pressure and obstruction at the level of the right ventricular outflow tract. This situation generates PH with increased right ventricular loading conditions. (14)

When present, a “splashing” auscultatory precordial sound, referred to as a millwheel murmur, is indicative of the presence of air within the cardiac cavities. Computed tomography is the diagnostic method of choice, showing an intracardiac image with air density. In experienced hands, transesophageal echocardiography is also an option for diagnosis.

The main goal of treatment is hemodynamic monitoring and support. An ample hydration plan should be maintained and, whenever possible, the patient should be placed in left lateral decubitus position trying to free the right ventricular outflow tract. Placement of a central venous catheter with the aim of aspirating air from the cavity may be a valid option when the amount of infused gas is considerable. On the other hand, the administration of oxygen at high concentrations (100%) may reduce the size of the bubble by increasing the nitrogen diffusion gradient. (15)

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