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REVIEW

Nonthrombotic pulmonary embolism

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ABSTRACT: Nonthrombotic pulmonary embolism (NTPE) is defined as embolisation to the pulmonary circulation of different cell types (adipocytes, haematopoietic, amniotic, trophoblastic or tumour), bacteria, fungi, foreign material or gas. The purpose of this article is to describe the clinical signs, pathogenesis, diagnosis and treatment of the different NTPE subtypes.

The complex and diverse pathogenesis of different subtypes of emboli is subject to continuing speculation and is certainly far more complex than ''simple'' mechanical obstruction after embolisation of vascular thrombi. Nonthrombotic emboli may also lead to a severe inflammatory reaction both in the systemic and pulmonary circulation, as well as in the lung.

NTPE presents a formidable diagnostic challenge, as the condition often presents with very unusual and peculiar clinical signs that are frequently overlooked. They range from very dramatic acute presentations such as acute respiratory distress syndrome to signs observed late in the disease course. Pathological observations play a key role in the exact diagnosis, and sometimes carefully aspirated blood from the pulmonary artery or specific staining of cells recovered from bronchoalveolar lavage fluid may be helpful. Frequently, lung biopsies revealing severe granulomatous reaction or unfortunate *post-mortem* pathological investigations of pulmonary tissue are necessary to confirm the diagnosis. Here, we also aim to familiarise the reader with the atypical radiological features of NTPE. Thin-section computed tomography of the lungs showing peculiar radiographic findings, such as a feeding vessel, the so-called tree-in-bud pattern or the appearance of micronodules distributed at the termination of bronchovascular bundles, may be observed in certain forms of NTPE.

Increased awareness of NTPE as an underestimated cause of acute and chronic embolism, which may result in acute and chronic pulmonary hypertension, is needed. Despite the fact that detailed descriptions of several forms of NTPE have existed for nearly 100 years, well-designed trials have never been performed to evaluate therapy in the different subsets of these patients.

KEYWORDS: Amniotic fluid, fat, gas, particulate material, pulmonary embolism, thrombotic *versus* nonthrombotic

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Unlike pulmonary thromboembolism, a frequently encountered cause of morbidity and mortality [1], nonthrombotic pulmonary embolism (NTPE) is less common. NTPE often presents with uncharacteristic clinical features and requires peculiar diagnostic measures and treatment options. Different cell types (adipocyte, haematopoietic, amniotic, trophoblastic or tumour), bacteria, fungi, foreign material and gas may be carried in the bloodstream and embolise to the pulmonary circulation (fig. 1). In contrast to ''ordinary'' thrombotic pulmonary embolism (PE), the effects of NTPE are not purely mechanical but are also linked to the nature of the embolic agent. This implies that the pathogenesis of NTPE is more complex than that of pulmonary thromboembolism and it is subject to continued speculation [2]. Nevertheless, NTPE can be associated with specific imaging findings, and familiarity with these features should facilitate prompt diagnosis [3]. This article reviews the features of acute and chronic NTPE.

FAT EMBOLISM

As early as in 1861, fat droplets were described in the lung of a railway worker who had sustained a crush injury [4]. Fat embolism (FE) is characterised by the release of fat into the systemic circulation. Fat embolism syndrome (FES) is a rare clinical consequence of FE, typified by the triad of pulmonary distress, mental status changes and a petechial rash [5].

Incidence

Disruption of sinusoids and fat in bone marrow allows fat globules and bone debris to gain access to the venous circulation. Embolisation of bone

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fat probably occurs in almost all patients who sustain a pelvic or long-bone fracture or undergo an endomedullary nailing of long-bone fractures or placement of knee and hip prosthesis [6]. An autopsy study of soldiers who died in the Second World War revealed a 65% incidence of pulmonary fat droplets [7]. 0.25–11% of patients who sustain a single long-bone fracture meet the criteria of FE [5, 8, 9]. FES is more frequent in patients with multiple fractures [10], with an incidence of 4.8–7.5% after bilateral femoral fractures [11]. FES is observed mostly after bone fractures of lower extremities, less frequently with upper extremity fractures, and rarely after rib fractures or vertebral injury [12].

FE is not limited to skeletal injury. It is the leading cause of respiratory deterioration in blast victims who survive [13]. As no evidence of myeloid tissue was found in lung sections from blunt trauma victims, it is believed that soft tissue is the source of FE in these cases [14]. The almost ubiquitous finding of FE in cases of natural death is attributed to resuscitative measures [15].

Other causes of FE include an intra-osseous infusion, bone marrow harvest and haemoglobinopathies such as sickle cell disease (SCD) [16–18]. Among the haemoglobinopathies, SCD is commonly associated with pulmonary consequences. Bone marrow necrosis after vessel occlusion and activation of the clotting system may lead to FE, accounting for 33% of sudden deaths in SCD patients with lung problems [19]. Among older patients and those with neurological symptoms, FES often progresses to severe respiratory failure. It has been described after autologous fat harvesting and periurethral injection to treat stress incontinence [20]. Other unusual causes include mobilisation of fat in viral hepatitis after pre-existing fatty liver [21], in pancreatitis [22], or from the subcutaneous region due to a liquefying haematoma. Both pulmonary thromboemboli and FE have been found in lethal cases after tumescent liposuction [23]. In view of the large number of patients who are treated with liposome-embedded drugs, reports of fatal FE caused by intravenous liposome drug delivery or *i.v.* hyperalimentation are debatable [24, 25]. In lymphangiography (a now largely abandoned examination), FE caused by oily contrast medium injected into the lymph vessels has been reported [26]. Occlusion of the lymphatics presumably forced the material to enter veins. Monooctanoin, a mixture of glycerol esters that was used to dissolve gallstones *via* intrabiliary infusion, has caused deadly fat-like embolisation after *i.v.* injection [27]. Accidental or intentional *i.v.* lipid overdose has been described after injection of peanut, olive or lamp oil [28]. Many preparations intended for intramuscular use only are indeed formulated with vegetable oils. Multiple mineral oil enemas in an infant with Hirschsprung's disease also led to mineral oil embolism [29]. Finally, FE has been described following injection of rice bran oil into breasts for the purpose of augmentation mammoplasty [30].

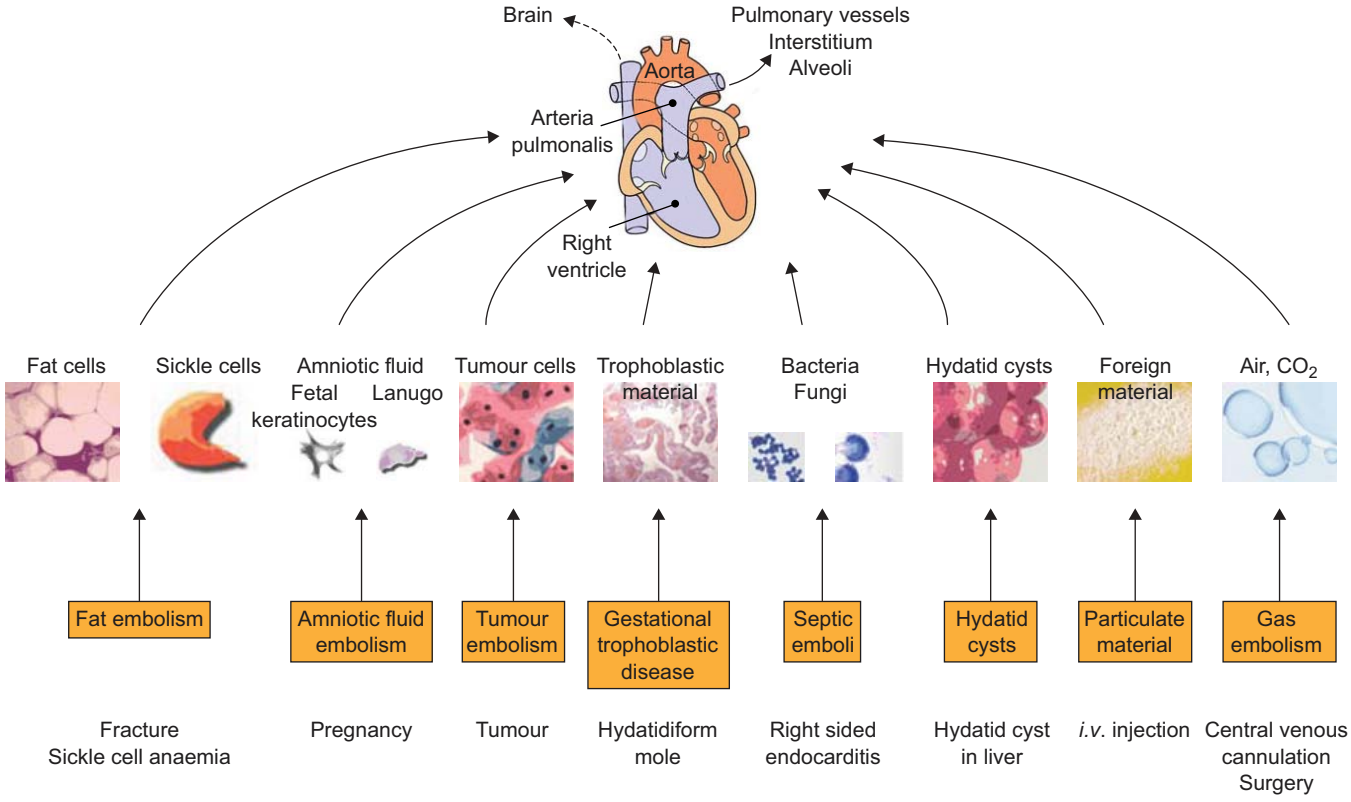

FIGURE 1. Nonthrombotic pulmonary embolism (NTPE) is characterised as embolisation to the pulmonary circulation of different cell types (adipocytes, haematopoietic, amniotic, trophoblastic or tumour), bacteria, fungi, foreign material or gas. NTPE presents a diagnostic challenge, as the condition often presents with very unusual and peculiar clinical signs that are frequently overlooked. They range from very dramatic acute presentations, such as acute respiratory distress syndrome (ARDS) after fat and amniotic embolism, to signs observed late in the disease course, such as after tumour emboli. Moreover, paradoxical nonthrombotic emboli may cause cerebral signs and symptoms.

Pathophysiology

The pathophysiology of FES remains largely unclear. Bone particles and fat globules are capable of physically blocking the capillaries of end organs including the lung [5]. The observation that the high content of fat in the lungs of injured patients has an identical free fatty acid (FFA) composition to that of bone marrow underlines this theory [31, 32]. Small fat droplets may even pass through lung capillaries and enter the systemic circulation [5].

The increase in bone marrow canal pressure during intramedullary instrumentation (*e.g.* nailing) can lead to ''intravasation'' of bone contents into the venous circulation [33]. The use of conventional cementing techniques is associated with echocardiographic evidence of embolism in 93% of patients [6]. The incidence of embolism is reduced with a modified technique that limits intramedullary pressure increases [6]. In animal models, a rinsing-suction-reaming procedure developed to lower pressure led to a significant reduction of fat intravasation compared to a universal reamer [34]. Intramedullary pressure increases significantly in reamed femoral nailing relative to unreamed [35]. Intraoperative prophylactic measures during hip arthroplasty can reduce the incidence of postoperative thrombosis and FE.

Fat globules may enter the systemic circulation through preexisting precapillary pulmonary or arteriovenous shunts (a patent foramen ovale), which allows showers of systemic emboli leading to obstruction of *e.g.* brain capillaries. Paradoxical cerebral FE must be considered in the differential diagnosis of altered mental status after fractures or joint replacement, and this condition may even occur despite a lack of a patent foramen ovale or a right-to-left intracardiac shunt [36]. Histological features consist of petechial haemorrhages throughout the cortical white matter and, to a lesser extent, the brainstem and spinal cord. It is unknown whether cerebral microemboli after total hip arthroplasty contribute to changes in postoperative cognitive function [37].

Even after a mild skeletal injury, there can be an interval of 24–48 h between the injury and the onset of FES. This delay cannot be explained by mechanical obstruction alone and there is no direct correlation between the amount of fat released and the severity of signs. In the early 1920s, a biochemical theory was introduced [5]. Fat emboli may initiate a biochemical and inflammatory cascade. Because pulmonary, renal and subchondral FE and fibrin thromboses are observed, it is suggested that injured marrow adipocytes release fat, thromboplastin and other vasoactive substances that conceivably play a procoagulant role in triggering disseminated intravascular coagulation (DIC). Fat emboli trapped in pulmonary vessels may be metabolised to FFAs and glycerol by lipase secreted by lung parenchymal cells [38]. FFAs induce endothelial and pneumocyte damage, capillary leak and clot formation. It is unclear why this cascade occurs in only some patients. Alternatively, circulating FFAs may originate from the breakdown of triglycerides at the fracture site or may become concentrated as a result of systemic lipolysis, induced by circulating catecholamines. The elevation of secretory phospholipase A2 (SPLA2) in patients with an acute chest syndrome in SCD, but not in patients with a vaso-occlusive crisis or non-SCD patients, suggests a role for SPLA2 in FE [39]. C-reactive protein may interact with circulating chylomicrons to form fat globules *de novo* [40]. FFAs are also capable of damaging cerebral cortical cells [5]. Further evidence for this theory is the observation that exposing neutrophils to oleic acid causes an increase in the cell surface expression and affinity state of the adhesion molecule CD11b, particularly under the acidic conditions that are typical of inflammation [41]. This might explain why trauma-induced release of fat causes pulmonary neutrophil accumulation [41]. In children, the fat content of the bone narrow is lower, and the composition (less of the toxic oleic acid) is different from that in adults, which might at least partially explain the lower incidence of FE in younger age groups [5].

Clinical signs

The clinical diagnosis of FES is one of exclusion, supported by laboratory and radiological investigations. GURD [42] and GURD and WILSON [43] outlined the classical signs and symptoms of FES; diagnosis is based on the presence of at least one of three major symptoms, four of eight minor symptoms and fat macroglobulinaemia. The major signs are respiratory distress, cerebral involvement unrelated to head injury and a petechial rash on the anterior surfaces of the neck, thorax or mucous membranes. The minor features are signs including tachycardia, pyrexia, retinal and urinary changes (anuria, oliguria or fat globules) and laboratory features including anaemia, thrombocytopenia or high erythrocyte sedimentation rate. Remarkably, the inclusion of fat globules in sputum as a minor criterion in the original paper [42] was replaced by jaundice in a second paper by the same group [43]. 60% of FES cases present with major symptoms within 24 h with a symptom-free period of at least 6–12 h after the initial trauma [44]. 75% of the patients develop pulmonary signs, but respiratory insufficiency requiring mechanical ventilation is rare [45]. Hypoxia-related tachypnoea, impaired oxygen diffusion, haemoptysis, combined respiratory and metabolic acidosis, chest pain, cyanosis and hypercapnia are also observed [5]. Rales and ronchi may be heard. FE is an indirect cause of ARDS [46].

Central nervous system signs range from encephalopathy to even a comatose state, not improving after correction of hypoxaemia, and may even occur with few or no pulmonary signs [47, 48]. Quadriplegia, convulsions and blindness have all been attributed to cerebral FE [49]. However, the neurological abnormalities are generally reversible. Fundoscopic evaluation may reveal macular oedema and retinal haemorrhages, and fat droplets may occasionally be seen in the retinal vessels [49]. In many cases, petechiae are only discovered after careful inspection of the axillae, the trunk, the neck, the conjunctival sac or oropharyngeal mucosa [8]. Petechiae are caused by fat globules that are carried by the bloodstream in the subclavian and carotid artery distributions. Because of their low specific density, fat globules cause petechiae on non-dependent, anterior skin areas when the patient is in a recumbent or (semi-) upright position. Skin biopsies have revealed coetaneous extravasations around capillaries blocked by fat and microinfarcts with fat [8]. These resolve in 5–7 days.

Diagnosis

Diagnosis is facilitated by the presence of haematological and biochemical abnormalities. Fat globules can be found in blood,

urine, sputum, bronchoalveolar lavage (BAL) or even cerebrospinal fluid (fig. 2a). Blood drawn from the femoral vein and examined cytopathologically may yield necrotic bone elements mixed with fat. Pulmonary microvascular cytology consisting of analysis of blood sampled while a Swan–Ganz catheter is in the wedge position has proven to be useful in diagnosing FE(S) [53, 54]. However, intravascular lipids can be shown relatively often, although only in patients who have received *i.v.* lipid emulsions [55]. Induced sputum analysis is also a safe and noninvasive test to detect FE in SCD [56].

To identify FFAs and fat, cells may be stained with techniques including Oil Red O, Nile blue or Sudan Black staining. The presence of lipid inclusions in alveolar macrophages is associated with various traumatic and nontraumatic conditions, particularly aspiration pneumonia and lipid infusions. BAL Oil Red O-positive macrophages are therefore frequently observed in the BAL fluid of trauma patients irrespective of the presence of FES [57]. To define FES, some authors have reported a cut-off of >5% of alveolar macrophages containing fat droplets, ranging 10–100% (median value 46%), in cases with proven or probable FE [58]. In another study, bronchoalveolar cells showed many large intracellular fat droplets (mean 63%; range 31–82%), whereas <2% of cells from trauma patients without FE or with non-FE-related ARDS contained such inclusions [59]. Others have proposed a threshold of 30% [60]. It is conceivable that a high number of Oil Red O-positive macrophages could also reflect clinically silent FE [57]. Alternatively, patients with FES showed an increase in the area of fat per alveolar macrophage [61]. Thus, automated semiquantitative analysis of fat within macrophages may be helpful in diagnosis but is not routinely available. Recently the most reliable parameter for *post-mortem* diagnosis was identified as the ratio of embolised tissue area to total tissue area [62]. As the presence of fat-containing macrophages in BAL fluid is not specific, serial changes in the percentage of these cells have been suggested to aid in the follow-up of disease severity. The levels of cholesterol (esters) in BAL can be used to distinguish patients with FES from other causes of ARDS. This is related to the activity of enzymes such as SPLA2 and platelet-activating factor (PAF)-acetylhydrolase [63].

In the early stage, atypical radiological findings are bilateral lung infiltrates (chest radiography) or consolidation and ground-glass opacities (computed tomography (CT)). We and others have described the high incidence of small (<1 cm), ill-defined centrilobular and subpleural nodules on CT in the acute phase of FES (fig. 2b). The nodules presumably represent alveolar oedema, micro-haemorrhage and an inflammatory response secondary to ischaemia [50, 64]. The dependent distribution of the nodules can be explained by the perfusion-related spread. Ill-defined centrilobular nodules have also been described in patients with acute pulmonary haemorrhage, related to the deposition of haemosiderin-laden macrophages

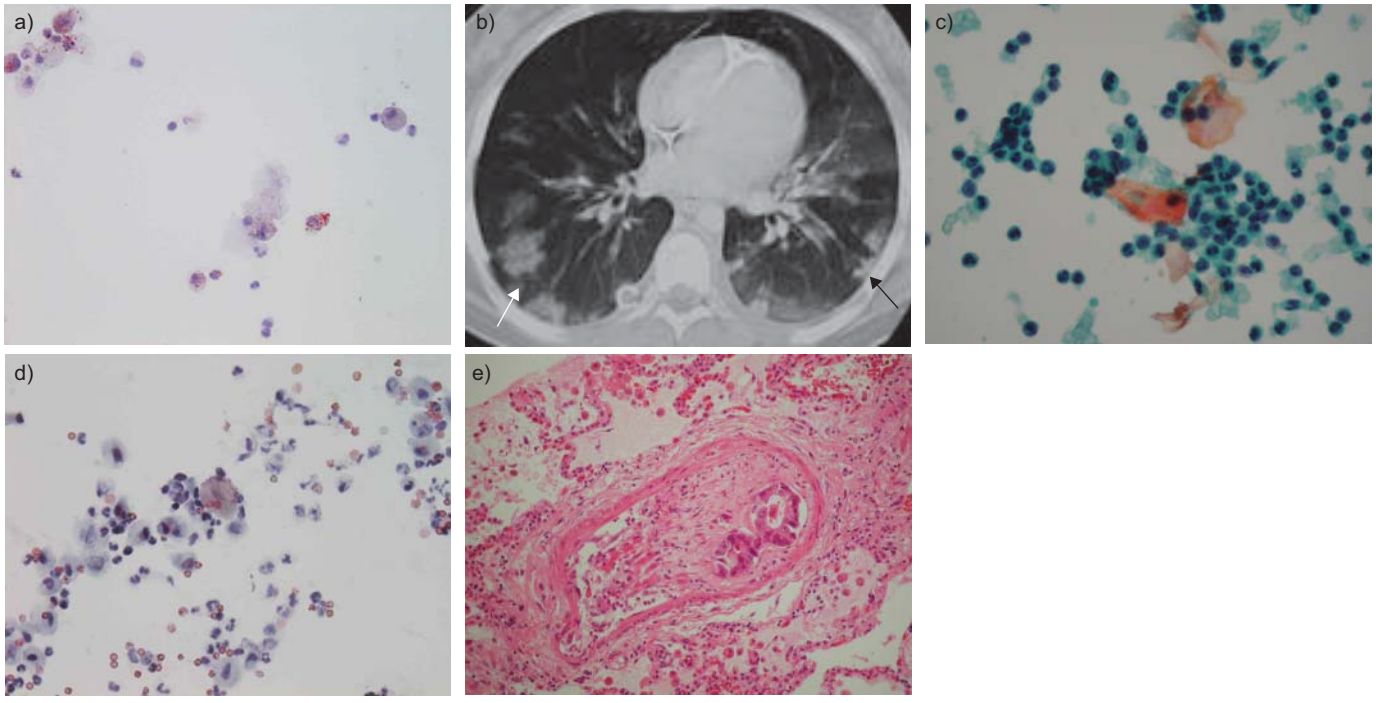

FIGURE 2. a) Massive fat embolism syndrome. Bronchoalveolar lavage (BAL) fluid (Oil-red-O staining) showing abundantly present lipid inclusions/fat droplets in alveolar macrophages (original magnification ×400). Reprinted from [50], with permission from the publisher. b) Computed tomography of the chest of a patient with proven fat embolism syndrome showing large ill-defined centrilobular airspace nodules and subpleural nodules (arrows). The nodules are predominantly of ground-glass opacity with some areas of soft tissue attenuation obscuring the edges of the vessels. Reprinted from [50], with permission from the publisher. c) Cytospin preparations (stained according to Papanicolaou's method) of a wedged pulmonary arterial blood sample showing the presence of fetal sqaumae/keratinocytes surrounded by platelets. Reprinted from [51], with permission from the publisher. d) Cytospin preparations (stained according to Papanicolaou's method) of BAL fluid showing fetal sqaumae in a background of inflammatory cells. Reprinted from [52], with permission from the publisher. e) Tumour embolism. Pulmonary artery branch with partially organised embolus containing two acini of adenocarcinoma. Autopsy specimen from a 74-yr-old man with a history of resection of a colonic adenocarcinoma 2 yrs previously (original magnification ×200).

[50]. Microhaemorrhages typically occur in FES by the local deposition and metabolisation of FFAs [65]. Diffuse lung calcifications located in the branches of the pulmonary arteries have been described in the late course of FES [65]. In patients with SCD, areas of ground-glass opacity are identified in segments with hypoperfusion. Denser areas of consolidation reflect either true infarction or infective consolidation [66]. Matching defects, especially in the upper half of the lung fields, are seen on ventilation/perfusion [67]. Magnetic resonance imaging (MRI) and magnetic resonance-spectroscopy [68] seem to be the most sensitive imaging technique for cerebral emboli, as T2-weighted MRI findings show nonconfluent areas of high intensity in watershed areas. Areas perfused by perforating arteries correlate well with the clinical severity of the brain injury [48, 69]. On the diffusion-weighted images, these lesions appear as bright spots on a dark background, a finding known as the ''Starfield pattern'' [48]. Cerebral microembolism can be monitored over time by detecting microembolic signals with transcranial Doppler [70].

Treatment

Treatment of FE should primarily be focused on prevention. Early immobilisation, open reduction and internal fixation of fractures, as well as methods to reduce intramedullary pressure during total hip arthroplasty, have reduced the incidence of FE [5]. Early femur fracture fixation (<24 h) is associated with an improved outcome, even in patients with coexistent head and chest trauma [71]. Delayed fixation increases the incidence of pulmonary shunting and pneumonia in patients with a high injury severity score and age >50 yrs [72]. When fracture stabilisation is delayed in patients with multiple injuries, the incidence of ARDS, FE and pneumonia, the costs of hospital care and the number of days in the intensive care unit (ICU) were increased [72, 73]. The exact method of fracture fixation, as opposed to the moment of fixation, plays a minor role in the development of pulmonary dysfunction [10].

FES is largely self-limiting and is usually associated with a good outcome. Current treatments are supportive: adequate oxygenation as well as haemodynamic stability, nutrition and prophylaxis of venous thrombosis and stress-related gastrointestinal bleeding. Therapy follows the same principles as management of ARDS. Transfusions and bronchodilators may improve oxygenation, and most patients who have even severe respiratory failure recover with aggressive treatment [16]. Several agents have been used in attempting to reduce the levels of circulating fat, including alcohol, heparin, low molecular weight dextran and aprotinin, but these are not currently recommended. A reduction was shown in the incidence of FES after administration of 10 $mg \cdot kg^{-1}$ methylprednisolone every 8 h, beginning in the emergency room [74]. A beneficial effect of 7.5 $mg \cdot kg^{-1}$ methylprednisolone given six times hourly for 3 days in patients at risk for FES has been reported [75]. However, the true beneficial effect of corticosteroids either before or after the development of symptoms has not been shown in a well-designed trial. High doses of N-acetylcysteine alleviated the pathological changes caused by FE in a rat model [76].

The successful use of veno-venous extracorporeal membrane oxygenation (ECMO) has been reported. ECMO support lasted ~120 h, followed by an uneventful recovery [77]. If a persistent foramen ovale is present, its closure before surgical manipulation of the fracture is feasible [78].

AMNIOTIC FLUID EMBOLISM

Although entry of amniotic fluid (AF) into the maternal circulation was first reported in 1926, it was not until 1941 that the importance of the condition was emphasised [79]. The presence of fetal debris in the pulmonary vessels of females who died during the peripartum period was then reported [80].

Incidence

The incidence of AF embolism (AFE) ranges 1 in 6,000–120,000 pregnancies [81–84]. AFE usually occurs during the immediate postpartum period [85]. Analysis of a national registry revealed that AFE occurred during labour but before delivery in 70% of cases and during caesarean section in 19% [86]. AFE has been reported as early as the second trimester. The diagnosis in cases occurring as late as 36 h postpartum is, however, debatable [87]. AFE following transabdominal amniocentesis is very rare [88]. Estimates emphasise that AFE has accounted for 12% of all maternal deaths related to legally induced abortion since 1972, with a death-to-case rate of 0.2 per 100,000 abortions [89, 90]. AFE is seldom associated with (surgical) manipulation during caesarean section [91], curettage [92], cervical suture removal [93] or repair of an incompetent cervix [93], or after car or motor vehicle accidents [94]. The 24 well-documented cases of AFE occurrence following (surgical) trauma have been recently reviewed [52]. At least 13 of these patients died of causes directly related to AFE [52].

Originally suggested [80] predisposing factors, such as advanced maternal age, multiparity and tumultuous labour, could not be identified by others [81, 86]. A large fetal size, use of oxytocics and vaginal prostaglandins, advanced gestational age, amnioinfusion or complicated labour have all been implicated [81, 95]. In reality, specific risk factors have not yet been conclusively identified. Logistic regression identified advanced maternal age, placental pathologies and caesarean deliveries in a large population-based cohort study [96]. The reported case fatality rate continues to be high: it might account for 10% of all maternal deaths in the USA. In the registry by CLARK *et al.* [86], the mortality was 61%; in a recent cohort study it was 21.6% [96]. There were only 39 survivors in another series of 272 cases, which indicates a mortality rate of 86% [81]. Among the survivors in the registry of CLARK *et al.* [86], only 15% were neurologically intact. All deaths occurred within 5 h of collapse, depending on the duration of resuscitation efforts. In a population-based study, maternal mortality rate (26.4%) was less than previously reported and might reflect a more accurate population frequency [84]. Of the 31 survivors of a UK registry, 12 women experienced cardiac arrest. Of the 13 women who died, seven of their babies survived [83]. Although there is still significant maternal and neonatal morbidity, the vast majority of women will nowadays survive [83].

Pathophysiology

The pathophysiological mechanism of AFE is poorly understood [82, 85]. Previous theories stated that the infusion of AF into the circulation occurred after tumultuous labour [80]. With

the evidence available today, these theories are indefensible. AFE may be related to the infusion of abnormal AF. Finding epithelial squames from the fetal skin in the pulmonary artery (PA) alone is not pathognomonic; rather, the combination of symptoms with detection of these cells is required [85]. Furthermore, there is not a clear temporal relationship between the entry of AF into the maternal circulation and symptom onset. AF may routinely enter the maternal circulation during delivery through open veins of the placenta or *via* tears in the lower uterus or cervix. Proposed mechanisms therefore include not only mechanical obstruction of the pulmonary vasculature by amniotic debris but also a reaction similar to septic shock [85]. The apparently idiosyncratic nature of the response and the presence of antigenic factors in AF has led some authors to propose AFE as an ''anaphylactoid syndrome of pregnancy'' [85]. This term implies that the severity of symptoms is related to the host reaction to a foreign antigen, driven by the antigenic potential of the AF. If AF composition determines this reaction, this might explain why women carrying a male fetus tend to be more frequently affected [86]. Similarly, meconium-stained AF may be more toxic than clear fluid.

AF is a complex mixture of maternal extracellular fluid and fetal urine, squamous cells, lanugo hairs, vernix caseosa, mucin and sometimes meconium [79]. Particulate matter originating from the AF has been identified at autopsy in the lung, kidney, liver, spleen, pancreas, brain and even retina [97, 98]. AF has no direct effect on the isolated human omental artery. The haemodynamic changes associated with AFE may therefore be due to secondary responses [99]. During labour, significant concentrations of prostaglandins appear. Other humoral factors, including proteolytic enzymes, complement factors, PAF, histamine, serotonin and leukotrienes, may contribute to the haemodynamic changes and consumptive coagulopathy associated with AFE. At autopsy, the pathological changes usually associated with DIC can be found in the many organs. Eosinophilic infiltrates have been reported in the lungs, hepatic portal fields and the heart, strengthening the theory of a hypersensitivity reaction [100]. Antitryptase staining of pulmonary tissue has revealed massive mast cell degranulation [101, 102]. Elevated serum levels of the neutral mast cell-derived protease tryptase add further supporting evidence for mast cell degranulation [103]. A numerical increase of pulmonary mast cells is seen in subjects who died of AFE, with values that correspond to those encountered in deaths due to anaphylaxis [101]. Serum tryptase and urinary histamine measurements were negative in another series but most women with AFE had elevated levels of fetal antigen [104].

Isolated DIC may be the first indication of AFE [105]. AF accelerates clot initiation and propagation. When AF is added to blood from pregnant women, the R time, which reflects the time to first clot formation, is significantly decreased with the addition of as little as 10 μL to 330 μL blood. This substantiates the hypothesis that coagulation profile changes are invariable accompaniments of AFE [106]. The Thrombelastograph® test may therefore be useful in assessing coagulopathy during or after AFE [107]. AF also contains large amounts of tissue factor (TF) pathway inhibitor (TFPI), accounting for virtually all of its coagulant potential. The intrusion of AF into the bloodstream may influence the plasmatic TFPI–TF equilibrium, which also results in DIC [108]. Isolated rat hearts perfused with varying concentrations of human AF also experience a dose-dependent decrease in coronary flow rate, rather than directly suppressing myocardial activity [109]. Several factors activated by AF have been shown to depress cardiac function [110].

Clinical signs

The condition can be neither predicted nor prevented. Probably the best diagnostic criteria focus on the constellation of signs and symptoms published in 1974 [111]. This was recently proposed in a slightly modified form: 1) currently pregnant or within 48 h of delivery; 2) one or more of the following observations severe enough to require medical treatment: a) hypotension; b) respiratory distress; c) DIC; or d) coma and/or seizures; and 3) absence of other medical explanations for the dramatic clinical course [112]. The presentation of AFE can be quite variable with respect to timing, symptoms and subsequent course: sudden onset of hypoxaemia and cardiovascular collapse are the main symptoms. These are often preceded by agitation, nausea or seizures. In 51% of cases, the presenting symptom is respiratory distress and isolated respiratory failure has been reported [105]. In the remainder, the first signal is hypotension (27%), coagulopathy (12%) or seizures (10%) [81]. Disturbances of coagulation, ranging from mild thrombocytopenia to overt DIC or isolated DIC without cardioplumonary instability, have been described. Two pregnancy-specific conditions of NTPE (choriocarcinoma and AFE) are rarely responsible for focal cerebral ischaemia, but global encephalopathy is not uncommon. A majority of AFE patients develop seizures and permanent neurological sequelae [85], due to impaired oxygen delivery to the brain [113].

Some patients are diagnosed with pulmonary oedema [51, 114, 115] and ARDS later in the course of the disease. Until recently, it was believed that the major haemodynamic change in AFE was the development of severe pulmonary hypertension due to critical obstruction and vasospasm of the pulmonary vessels, as suggested in animal models. Several reports suggest, however, the presence of severe transient left ventricular failure. PA catheter readings in human AFE cases frequently show low cardiac output and elevated pulmonary capillary wedge pressure as well as low left ventricular stroke work index [51]. A biphasic pattern of haemodynamic changes has therefore been postulated to reconcile the data, in which a first transient period of cor pulmonale exists, followed by left heart failure [115]. There are no clear human data confirming this biphasic pattern. In 1990, the haemodynamic data were reviewed indicating that left ventricular dysfunction was present with secondary mild-to-moderate increase in PA pressure in all available cases [85]. We recently reviewed all 18 well-documented cases of left ventricular failure after AFE. In five out of these 18 reported courses, the left ventricular failure contributed to the fatal course [51].

Diagnosis

AFE is again a diagnosis of exclusion. Identification of squamous cells in the maternal pulmonary arterial circulation, either at autopsy or *intra vitam*, was originally regarded as pathognomonic (fig. 2c) [51]. Finding fetal elements in the PA can only be considered supportive. Squamous cells can appear in the

pulmonary blood of heterogeneous populations of pregnant and nonpregnant patients [115], also resulting from contamination by exogenous sources during specimen preparation or derived from the entry site of the PA catheter [116]. Trophoblastic cells are free-floating in the intervillous space and have direct access to the maternal circulation. Therefore, blood from the PA should be collected as described by MASSON and RUGGIERI [117] and MASSON [118]. In order to minimise the possibility of contamination, a representative sample could be obtained if blood is drawn from the distal lumen of a wedged PA catheter. After discarding the first 10 mL, an additional 10 mL is drawn, heparinised and analysed utilising Papanicolaou's method [119]. Reliable differentiation of adult from fetal squamous cells is not possible; however, the significant increase in cell count documented in pregnant patients suggests a possible fetal origin for some squamous cells detected during pregnancy. In a critically ill obstetric patient, squamous cells in the pulmonary vessels should not deter the clinician from a search for other causes of instability [115].

Squamous cells coated with neutrophils or thrombocytes, accompanied by fetal debris, or eosinophilic granular material with adherent leukocytes are considered more likely to be found in AFE (fig. 2c) [117, 120]. The diagnosis may be further supported by the presence of amniotic cells in BAL fluid (fig. 2d) [52]. Rhodamine B fluorescence may identity sparsely distributed fetal squames that otherwise may be overlooked by less sensitive tinctorial methods [121]. Detecting the simultaneous presence of syncytiotrophoblast cells and megakaryocytes in the pulmonary microvasculature by means of a panel of monoclonal (CD61-GpIIIa, beta-hCG) and polyclonal (FVIII-vW, hPL) antibodies allowed the confirmation of AFE [122]. The staining of fetal isoantigen or staining with an antibody raised to human keratin have all been described [123]. Immunohistochemical staining with the sensitive monoclonal antibody TKH-2 against a common fetal antigen (Sialyl Tn, NeuAc alpha 2-6GalNAc) had a high sensitivity for diagnosing AFE [124]. AFE can indeed be easily missed on haematoxylin and eosin sections. As Alcian blue staining may also be insufficient to show intravascular mucin in the maternal lung sections, TKH-2 immunostaining is a more sensitive method to detect AF-derived mucin in lung sections [125]. Measuring zinc coproporphyrin I, a characteristic fetal-gut component of meconium, in maternal plasma may be a sensitive method to diagnose AFE [126].

Chest radiography reveals diffuse bilateral homogeneous opacities [2]. Because AFE is characterised by the absence of frank pulmonary vessel obstruction, it has only been occasionally reported to present with the obstruction of branches of the PA during angiography [127]. Transoesophageal echocardiography may reveal enlargement of the right ventricle and main pulmonary trunk, consistent with acute right ventricular pressure overload, but also full-blown left ventricular failure in view of the depression of left ventricular function [51].

Treatment

AFE can be neither predicted nor prevented so randomised controlled trials are not possible. The maternal and fetal outcome is unpredictable. The majority of patients will require ICU admission [113]. Management is directed towards the maintenance of oxygenation, circulatory support and correction of the coagulopathy. Mechanical ventilation can be necessary to maintain oxygen supply as well as invasive monitoring to guide the use of inotropic agents and fluid. Optimisation of cardiac preload by volume expansion in hypotension and inotropic support is indicated if (left) heart failure is observed [51, 114]. In some cases, after-load reduction may be beneficial in restoring cardiac output, providing pre-load is adequately preserved. Diuretics are useful to mobilise pulmonary oedema.

In 65% of AFE cases, delivery had not yet occurred. Immediate delivery of the fetus by caesarean section is mandatory to prevent fetal hypoxic damage and facilitate resuscitation [82]. Case reports have highlighted the importance of displacing the uterus laterally to avoid compressing large vessels and even performing an emergency caesarean section during resuscitation [128]. Treating the coagulopathy involves the administration of blood components. Cryoprecipitate is rich in fibronectin, which aids the reticulo-endothelial system in the filtration of antigenic matter. Historically, depleted levels of this glycoprotein have been reported, with improvement following repletion of fibronectin levels [129]. The successful use of activated recombinant factor VIIa in the management of severe haemorrhage secondary to AFE has been reported [130]. Leukocyte depletion filtering of cell-salvaged blood obtained from caesarean section might reduce particulate contaminants to a concentration equivalent to maternal venous blood [131]. Several studies have revealed no increased risk of complications after autologous blood autotransfusion during caesarean section.

Novel therapies have been described anecdotally. Successful haemorrhage management may be further optimised by uterine artery embolisation, thus avoiding hysterectomy [132]. Plasma exchange transfusions, continuous haemofiltration and aprotinin administration have been attempted [86, 133], as has the use of nitric oxide or inhaled aerosolised prostacyclin to treat hypoxaemia [134, 135]. In light of the similarities to anaphylaxis, corticosteroids and epinephrine have been suggested as useful therapeutic adjuvants [86]. ECMO and intra-aortic balloon counterpulsation might be considered in left ventricular failure unresponsive to medical therapy [136]. The successful treatment of a moribund patient with cardiopulmonary bypass and PA thromboembolectomy has also been shown [137].

TUMOUR EMBOLISM

The lung is a target of remote malignancy: embolism to the pulmonary vasculature is obviously a prerequisite for the development of metastasis but has rarely been described as a distinct entity. Pulmonary tumour embolism (PTUE), characterised by the occlusion of pulmonary vessels by tumour cells, was described more than 100 years ago [138]. It was not until 1937 that cor pulmonale due to emboli to the pulmonary microvasculature was described [139].

Incidence

Macroscopic PTUE has been reported in sarcomas, hepatocellular, breast and renal cell carcinomas, whereas microscopic PTUE was found predominantly in gastric, hepatocellular and pancreatic carcinomas and choriocarcinomas It has also been described in patients with lung, prostate, thymic, gall bladder, bladder, colorectal, skin or cervical cancer [140–143].

Pulmonary hypertension may be seen occasionally as a consequence of capillary plugging by malignant megakaryocytes in essential thrombocytopenia. Tumour emboli might occur subclinically and were seen microscopically in 2.4–26.0% of autopsies of patients with a solid malignancy [144–147]. In a review of 1,069 autopsies, three cases in which death had occurred from cor pulmonale due to tumour embolisation from breast, lung, and ovarian carcinoma were observed [148]. Tumour macroembolism is also reported in the setting of sudden death requiring medicolegal investigation [149]. It should be distinguished from primary tumours arising from the intima of the PA, such as malignant fibrous histocytoma or sarcoma [150].

Pathophysiology

Macroembolism is a feature of primary tumour sites that are connected by the vena cava to the right ventricle [151]. Tumour emboli possess an unusual level of resistance to recannulation and are therefore more likely to lead to progressive, irreversible obstruction. Most cases of microembolism show a vascular tissue reaction with intimal proliferation and fibrosis (fig. 2e); bland tumour emboli without or with only scarce vascular reaction are rarely seen [140, 152]. In PTUE, anywhere from 7–81% of the pulmonary arteries contain emboli [147]. The extent of the occluded cross-sectional area of the pulmonary arterial bed determines the increase in pulmonary vascular resistance and explains why only some patients become symptomatic. There is usually no marked cardiopulmonary functional derangement until 60–80% of the pulmonary arterial bed has been occluded. At some degree of obstruction, the ability of the pulmonary vasculature to adapt is impaired [153].

Platelets and thrombin are frequently present in addition to malignant cells. As organisation of the thrombus occurs, the embolic cancer cells degenerate. Fibrocellular intimal hyperplasia and fibrosis of pulmonary arteries may occur with smooth muscle colonisation of the luminal neoplastic lesions, both adjacent to emboli and in vessels where emboli are not seen [145, 154]. PTUE is different from a haematogenous, true metastasis, as there is no tendency for the tumour emboli to invade the arterial wall [141, 146]. Tumour emboli are destroyed or remain latent intraluminally [141]. The eventual outcome of malignant cells in the lung (metastasis, invasion of lymphatics, development of pulmonary hypertension or clearance of the cells) is the result of interactions between signalling pathways that affect angiogenesis, apoptosis and inflammation. Necropsy series [146, 147] suggest that there are four types of pulmonary involvement: 1) large tumour emboli occlude the pulmonary arteries; 2) microscopic tumour emboli involving the small vessels account for subacute pulmonary hypertension found in the majority of cases; 3) pulmonary microvascular invasion may be part of the generalised lymphatic involvement, which explains the diffuse interstitial infiltrates seen in some cases; and 4) pulmonary tumour embolism can be caused by a combination of the above mechanisms [141, 153].

Clinical signs

Pulmonary tumour microembolism may be suspected in patients who complain of unexplained dyspnoea and develop cor pulmonale. The most common symptom is subacute progressive dyspnoea which occurs in 57–100% of cases over a span of weeks to months [141, 147, 153], as well as pleuritic chest pain, cough, haemoptysis and weight loss [2]. In a retrospective review of 164 cases, a typical profile of features was reported: documented or suspected underlying malignancy, acute-to-subacute onset of dyspnoea and signs of cor pulmonale [141]. Retrospective chart reviews demonstrate that only 8% of patients with pathological evidence for PTUE have documented morbidity or mortality attributable to the emboli: the ''classic,'' signs of right heart failure are reported in only 15–20% of patients [148, 155].

Arterial blood gas measurements invariably show hypoxia, usually hypocapnia or increased alveolar–arterial oxygen gradient [141]. In many instances, metastases to other organs were documented prior to the onset of respiratory symptoms. However, PTUE as the initial manifestation of underlying malignancy was also reported in a few patients [141].

Diagnosis

Tumour macroembolism is clinically indistinguishable from thromboembolism, and the diagnosis is therefore achieved mostly through autopsy [140]. The presence of both thrombotic and tumour PE should be considered in all cancer patients because of similarities [156]. Even in patients known to have a malignancy, the correct diagnosis is made in as few as 6% *ante mortem* [145]. Moreover, PTUE has a lack of specific radiological features and mimics pneumonia or interstitial lung disease. A normal chest radiograph with hypoxaemia in a patient with a malignancy might even suggest the presence of PTUE: only one out of eight patients had a parenchymal abnormality on a plain radiograph [147]. Cardiomegaly and prominent pulmonary vasculature, the radiographic changes associated with elevated pulmonary pressures, are seen in $<$50%. In an attempt to distinguish carcinomatosis and tumour emboli, some investigators suggest that lymphatic disease is more likely to have an interstitial infiltrate.

Subsegmental, mismatched peripheral defects have been described on ventilation–perfusion in patients with exclusively microvascular disease [157]. The ventilation scan is usually normal [141]. Tumour emboli are usually located in small or medium arteries so angiography, the gold standard for thromboembolic disease, has poor sensitivity and specificity for detection: ''typical'' pulmonary angiographic findings include delayed filling of the segmental arteries, pruning and tortuosity of the third- to fifth-order vessels. The CT findings further include multifocal dilatation and beading of the peripheral subsegmental arteries and peripheral wedge-shaped areas of attenuation due to infarction [158]. However, most patients have no evidence of embolic disease by pulmonary angiogram [159]. The tree-in-bud pattern is commonly seen on thin-section CT of the lungs, and it consists of small centrilobular nodules of soft tissue attenuation connected to multiple branching linear structures of small calibre that originate from a single stalk [160]. Originally described in cases of endobronchial spread of *Mycobacterium tuberculosis*, it is now also recognised as a manifestation of PTUE [161].

The use of transoesophageal echocardiography, accurately defining the cephalad extent of the thrombus, might be

considered in diagnosing and guiding intraoperative management of a migratory embolus from the inferior vena cava. Radiolabelled monoclonal antibody imaging and repeated pulmonary microvascular cytology sampling techniques were historically promising diagnostic tests [141]. Obtaining a suitable sample of blood from the pulmonary capillary bed for tumour cells again requires that blood be aspirated from the distal port while the catheter is in the wedged position to avoid malignant cells from ''upstream'' (*e.g.* the liver) contaminating the sample. Blood is subsequently either filtered or spun down, and the remaining cells stained with the Papanicolaou method. The interpretation of such samples proves to be challenging, as megakaryocytes and endothelial cells may mimic malignancy [162].

Treatment

The prognosis is poor and the median survival from diagnosis is a few weeks. In view of these patients' likely prognosis, interventions to cure or slow down the progressive deterioration are rarely performed. The principal intervention in most cases was surgical resection of the primary neoplasm, if possible. Surgical cure by resection of the primary tumour has been reported in patients with atrial myxoma, renal cell carcinoma and choriocarcinoma [141]. Chemotherapy is rarely indicated, although favourable results have also been reported in patients with choriocarcinoma and breast cancer [159].

TROPHOBLASTIC MATERIAL FROM GESTATIONAL TROPHOBLASTIC DISEASE

Incidence

Gestational trophoblastic disease (GTD) defines a heterogeneous group of inter-related lesions arising from abnormal proliferation of the trophoblastic epithelium of the placenta. Two subtypes arise from an aberrant fertilisation (complete or partial hydatiform mole) and three malignant subtypes (invasive mole, choriocarcinoma and placental site trophoblastic tumours) may occur after any gestational experience [163]. Trophoblastic embolism may be subclinical in normal pregnancy and more pronounced in eclampsia. It also occurs within hours following abdominal hysterectomy for invasive moles, molar evacuation and as a side effect of chemotherapy for choriocarcinoma [164–166].

Pathophysiology

The pathogenesis is unique because the tumour arises from fetal, not maternal, tissue. The question has been raised whether trophoblastic embolisation is an entity that occurs independent of pulmonary oedema (a sequel of accompanying hyperthyroidism), pre-eclampsia and fluid overload or whether discovery of trophoblastic tissue in the lungs is merely coincidental [167]. Even when a mass of molar tissue is gently manipulated, there is a risk of pulmonary trophoblastic emboli. On the other hand, although multinucleated giant cells and large mononuclear cells are identified in the buffy coat of blood aspirated before and during evacuation of large molar pregnancies, no significant changes in mean systemic arterial, pulmonary arterial or capillary wedge pressures were seen. Likewise, cardiac output and pulmonary vascular resistance were mostly unchanged. When significant decreases in haemodynamic variables were observed during evacuation, these returned to pre-evacuation levels after completion of anaesthesia [164]. This indicates that trophoblastic embolisation sufficient to cause severe pulmonary compromise is rare.

Clinical signs

Vaginal bleeding is the most frequent symptom of GTD. Self-limited respiratory distress arises in 3–10% following molar evacuation, with the number rising to 25% when the uterus is larger than predicted for the gestational age and the human chorionic gonadotropin level exceeds 100,000 $mIU \cdot mL^{-1}$ [168]. The acute illness, which requires aggressive support, lasts 24–48 h. This is typically followed by a dramatic clinical improvement over the following 48–96 h, with pulmonary function returning to baseline generally within 72 h [168]. Due to the routine use of ultrasound and beta-hCG in the workup of early gestational abnormalities, complete molar pregnancy rarely presents today with the traditional signs although the potential for persistent trophoblastic disease still exists [169]. Pulmonary trophoblastic embolism is infrequently associated with sudden death [166, 170].

Diagnosis

Pulmonary involvement occurs in up to 80% of women with metastatic GTD [171]. Radiographic findings are variable and include alveolar, nodular and miliary patterns, pleural effusion and signs of pulmonary arterial occlusion [165]. Again, some authors have demonstrated syncytiotrophoblast and multinucleated trophoblastic giant cells in pulmonary arterial blood sampled during molar evacuation [164, 172].

Treatment

Management of trophoblastic embolisation is no different from that of other causes of hypoxaemia and NTPE. Infusions of fluid and blood tend then to cause pulmonary overload, which may precipitate heart failure. Preferred therapy consists of diuresis and ventilatory support [167]. Emergency pulmonary embolectomy under cardiopulmonary bypass has been reported for an embolism of malignant trophoblastic material [173].

SEPTIC EMBOLI

Incidence

Septic pulmonary embolisation (SPE) is a rare but well-recognised problem in the setting of right-sided endocarditis and septic thrombophlebitis from such sources as the tonsils, the jugular, dental or pelvic region and infected central venous catheters [174, 175]. SPE is becoming an uncommon complication of *i.v.* drug use, presumably due to greater needle hygiene [176]. The increasing use of long-term indwelling catheters or prosthetic vascular devices as well as increasing numbers of immunocompromised patients have changed the epidemiology [176]. In children too, soft tissue infection, osteomyelitis and *i.v.* catheters have been recognised as risk factors [177].

In a huge series of *post-mortem* examinations in Japan, SPE was found in 2.2% of 11,367 cases of ''critical'' pulmonary embolism [178]. Infectious endocarditis was responsible for 11% of these cases of SPE. Surprisingly, fungal emboli (from *Aspergillus, Mucor* or *Candida*) were found more frequently than bacterial: most of these fungal emboli had a (haematological) malignancy as the underlying risk factor [178]. This is in contrast with a low incidence of reported cases of *Aspergillus* tricuspid endocarditis [179].

A peculiar subtype is Lemierre's syndrome (postanginal sepsis), an anaerobic thrombophlebitis of the internal jugular vein with metastatic infection. Most patients affected are young adults with tonsillopharyngitis, odontogenic infection, mastoiditis or sinusitis. The causative organisms include the anaerobic gram-negative *Fusobacterium* species, but also *Eikenella, Porphyromonas, Streptococci* and *Bacteroides* [180, 181]. Recently, methicillin-resistant *Staphylococcus aureus* has been identified as a new causative agent [182]. Extension of the infection to the adjacent lateral pharyngeal tissue results in haematogenous spread. Pulmonary involvement in Lemierre's syndrome has been reported in up to 97% with lung abscesses and empyema [183].

Pathophysiology

Septic pulmonary emboli reach the lung from many sources, including infected heart valves, thrombophlebitis and infected catheters or pacemaker wires [180, 184]. In tricuspid endocarditis, local infection can produce typical cystic lesions, often complicated by empyema. A thrombus containing microorganisms embedded in fibrin mobilised from an infectious nidus is implanted in the pulmonary arteries, leading to an infarction inciting a metastatic abscess (fig. 3a) [176, 185]. Cavitary parenchymal nodules may be caused by septic occlusion of small peripheral PA branches [186]. Pulmonary infarction is uncommon when the emboli obstruct the central arteries but is frequent when distal arteries are occluded [187]. This may be explained by collateral flow from the bronchial arterial circulation that enters the PA distal to the site of an obstruction [186]. Peripheral parenchymal consolidation (wedge-shaped lesions) is then partially caused by pulmonary haemorrhage from the extravasations of the bronchial arterial flow [188].

Clinical signs

The characteristic features are a febrile illness, cough, haemoptysis and lung infiltrates associated with an active focus of extrapulmonary infection [176, 189].

Diagnosis

Clinical and radiological features at presentation are nonspecific, and the diagnosis is frequently delayed [176]. Blood cultures, chest CT and echocardiography are invaluable when evaluating a patient with suspected SPE [176]. Transoeasophageal echocardiography provides greater spatial resolution compared with transthoracic imaging and is a superior method for imaging vegetations, abscesses and leaflet perforations [190]. Typical radiographic features include patchy air space lesions simulating nonspecific bronchopneumonia, multiple ill-defined round or wedge-shaped densities of varying sizes located peripherally and lesions abutting the pleura and located at the end of vessels (feeding vessel sign) scans [177, 184] (fig. 3b). This feeding vessel sign has also been reported in both uncomplicated pulmonary emboli and pulmonary metastases and simply indicates the haematogenous origin of the parenchymal nodule [184, 191]. Transverse images showed that 37% of the nodules and 22% of the wedge-shaped opacities in SPE had a vessel that appeared to enter the nodule, although both multiplanar reconstructions and maximum-intensity projections showed that the vessels passed around the nodules [191]. All of these vessels were traced to the left atrium, a finding consistent with pulmonary vein branches [191]. Multi-detector CT is superior to the classical CT technology for detection of this feeding sign. Rapid progression of the lesions to cavities or abscess formations can occur [177].

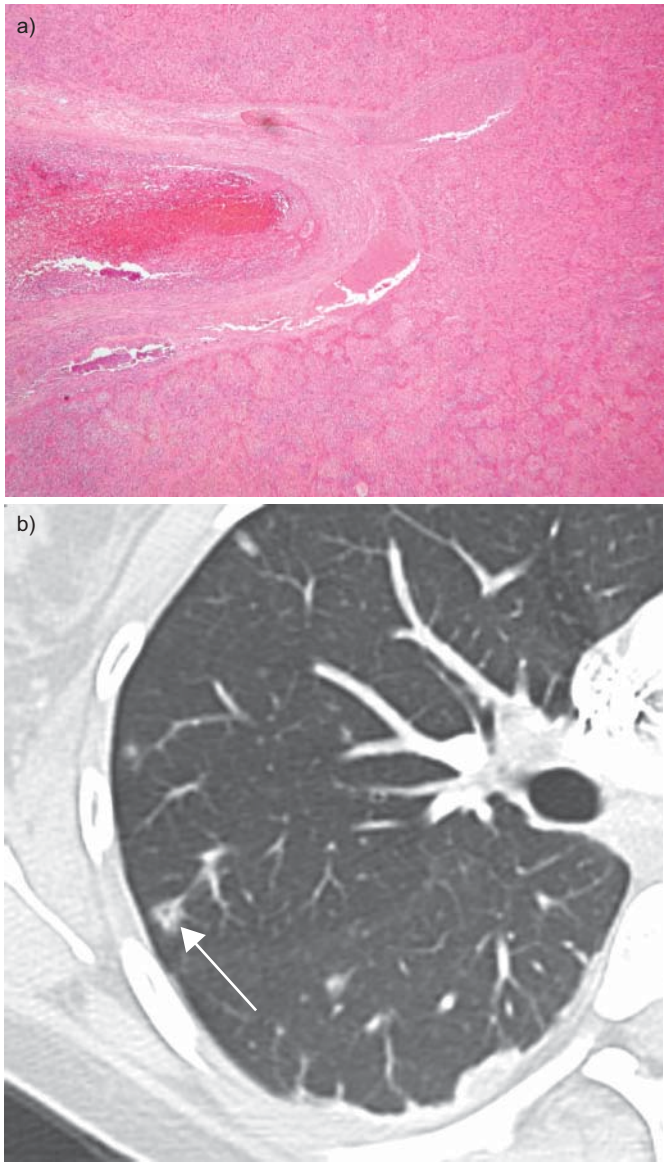

FIGURE 3. Septic embolism. Lung infarction by a septic thrombus from the tricuspid valve in a 21-yr-old female with endocarditis. Repeated blood cultures and culture of the valve disclosed a positive culture for *Staphylococcus aureus*. a) A haematoxylin- and eosin-stained section of this infarcted lung specimen shows the obstructed large pulmonary artery branch and surrounding lung tissue with coagulation necrosis (original magnification ×40). b) Chest computed tomography of this patient with endocarditis of the tricuspidal valve and pulmonary septic emboli. Axial computed tomography showing multiple irregular nodules of which some are cavitated. Moreover, feeding vessels are demonstrated leading directly to a subpleural cavitated nodule in the right upper lobe (white arrow).

It is noteworthy that KWON *et al.* [185] recently reported that the size of the nodules in gram-positive septic emboli was larger than those in gram-negative. Cavitation and air bronchogram within the nodules were seen more frequently in the gram-positive emboli, while a ground-glass attenuation halo around a nodule and a feeding vessel sign were more commonly observed in gram-negative emboli. Hemorrhagic nodules have

a characteristic, although nonspecific, CT appearance that consists of a central area of soft tissue attenuation surrounded by a halo of ground-glass attenuation, termed the CT ''halo'' sign. This sign can be caused by several pathological processes and is found in haemorrhagic pulmonary nodules as well as nonhaemorrhagic inflammatory lesions [192, 193].

Treatment

Septic patients are also at risk of thrombotic pulmonary embolism [194]. The management of a free-floating (even septic) thrombus in the femoropopliteal or iliocaval veins is therefore controversial. Although the deployment of inferior venal caval filters is of theoretical benefit, the uncertainty of their potential adverse event profile has limited their current use. Although debated [194], it is usually proposed that venal caval filters should not be implanted in patients with risk of septic embolism. [195].

In 1978, MACMILLAN *et al.* [189] described 60 patients with SPE: *i.v.* drug users comprised 78% of their cohort, and tricuspid endocarditis was the embolic source in 53%. At that time, 20% still required thoracotomies to manage lung abscess, bronchopleural fistula and empyema [189]. Recent studies demonstrate improved outcomes for patients with SPE with virtually all patients recovering from their illness. This may be attributable to earlier diagnosis, prompt administration of broad-spectrum antibiotics and improvements in surgical and supportive care [176, 196]. High doses of *i.v.* antibiotics targeting anaerobic organisms in Lemierre's syndrome are indicated [197].

HYDATID CYSTS

Incidence

Cystic hydatid disease or echinococcosis is a parasitic infection caused by the larval or cyst stage of the tapeworm *Echinococcus granulosus*. Humans can be infected by ingesting eggs, from which cysts develop in the liver and lung. Echinococcosis is mostly endemic in sheep-farming areas of the Middle East, South America, Oceania and along the Mediterranean coast [198].

Pathophysiology

The parasite can reach any part of the body, although the organs most commonly affected are the liver (75%) and lungs (15%) [199]. The embryo rarely reaches the right heart cavities through the portal or lymphatic routes. Hydatic PE occurs after rupture of a hydatid cyst in the right ventricle or atrium, or more rarely haematogenous dissemination from a hepatic focus rupturing into the hepatic veins or the inferior vena cava [200, 201]. Autopsy findings indicate that embolism is caused by vesicles or cysts that act purely mechanically by obstructing the blood flow, as there are no blood clots or added thrombosis [202]. Hydatid cysts may rarely present in the wall of the arteries [200, 201].

Clinical signs

The major complication is rupture of the cyst into the pericardium, which can lead to anaphylactic shock or tamponade [200]. The clinical manifestations of pulmonary arterial hydatid cyst embolisation are not specific, although haemoptysis is the most frequent sign [203, 204]. It is classified according to the clinical presentation: 1) acute fatal cases; 2) subacute pulmonary hypertension with death in less than a year; and 3) chronic pulmonary hypertension [3]. The majority of cases appear to follow a course of prolonged pulmonary hypertension punctuated by acute embolic episodes [204, 205]. A cardiac hydatid cyst that caused complete occlusion of the right PA has been described [205]. Seldomly, a primary interventricular cyst may rupture *via* the pulmonary veins, resulting in multifocal pulmonary cystic lesions [206].

Diagnosis

The diagnosis is difficult in the absence of typical clinical and radiological findings. Serological tests, though more specific than imaging techniques, are less sensititve but are useful confirmatory tests [207]. Diagnosis, guided by echocardiographic findings, is mostly based on the arteriogram, revealing segmental or lobar perfusion defects [208]. Some authors have emphasised the role of combined contrast-enhanced spiral CT, MRI and pulmonary magnetic resonance angiography of the chest to evaluate complicated cardiac hydatid cysts. Echinococcal embolisation to the PA has also been studied with these techniques in the absence of intracardiac and hepatic hydatid cysts [203]. On enhanced CT, the intra-arterial cyst shows a typical hypodense appearance [203].

Treatment

When a right-sided cardiac hydatid cyst is diagnosed, early surgical treatment should be performed under open-heart surgery conditions [198]. Median sternotomy and the use of extracorporeal circulation must be the surgical approach of choice when cysts are present in the cardiac chambers [202]. Embolectomy by removing multiple fragments of a ruptured endocyst of the PA, followed by surgical closure of the cardiac cyst cavity, can be performed [209]. Surgical intervention can be complicated by rupture of the artery and/or the cyst. Dissemination of the disease, anaphylactic shock and pseudoaneurysm formation can then occur [203]. Surgical treatment combined with chemotherapy may improve the prognosis [200]. Medical therapy is advocated for patients with recurrent hydatidosis or in those where surgical intervention involves a high risk. This poor prognosis depends on the patient's general status as well as the number and size of the embolised vessels.

PARTICULATE MATERIAL

Incidence

The *i.v.* injection of illicit drugs or drugs intended for oral administration is associated with a variety of pulmonary consequences. Some of these oral medications, including amphetamines, methylphenidate, methadone, meperidine, pentazocine, hydromorphone and dextropropoxyphene, are ground by drug users, mixed in liquid and then injected intravenously [210, 211]. The *i.v.* abuse of pharmaceuticals such as codeine and temazepam has also been reported [212].

Other emboli-causing substances including talcum, starch, cellulose and cotton may be observed in individuals who engage in *i.v.* drug abuse or parenteral injection of these tablets. Substances such as magnesium trisilicate, corn starch and microcrystalline cellulose are used as fillers and binders during manufacturing [213]. Pills, containing both active drug and fillers, are crushed and dissolved in water by heating the mixture. This solution is drawn into a syringe using cotton as a filter before injection. When the supply of available drug is exhausted, addicts may heat the cotton balls in water to draw

any trapped drug back into solution [210]. Similar emboli can also occur in the hospital when cotton fibres remain on angiographic guide wires or catheters after they have been wiped with moist cotton gauze [214]. The nature of the material in lung tissue from 33 addicts appeared to be birefringent material in 31 cases, with talcum being the only material in eight cases or in conjunction with other materials in all remaining cases [215]. Crospovidone, an insoluble polymer used as a disintegrant, can also embolise when tablet suspensions are injected [216].

Catheter emboli are rare iatrogenic complications as they usually develop when a physician attempts to withdraw a catheter through an introducing needle. The catheter catches on the needle, and the distal portion is sheared off. Spontaneous catheter breakage accounts for 25% of catheter emboli. Most catheter emboli are found in the basilic vein and the pulmonary arteries, with the remainder in the right heart, great veins and peripheral lungs [217]. Cannulation of antecubital, subclavian, femoral and internal jugular veins, as well as cardiac catheterisation and temporary pacemaker insertion have all been associated with embolisation [218]. Central embolisation of needle fragments has also been reported in *i.v.* drug abusers [218].

A great variety of materials can embolise. Teflon from an eroded valve has been found in the vessel walls and parenchyma of the lung [219]. Pulmonary emboli caused by accidental or intentional *i.v.* injection of metallic mercury (fig. 4) have been encountered [3, 220]. Liquid silicone, an inert material used for medical purposes but also during illegal cosmetic procedures in women and transsexual men, may embolise [221]. Patients with arterio-venous malformation (AVM) undergo endovascular treatment with embolisation of different materials, including cyano-acrylate agents, polyvinyl alcohol foam particles, microcoils, silk or dacron thread and balloons [222]. Three out of 182 patients who had undergone embolisation of brain AVMs with cyano-acrylate, developed pulmonary symptoms due to embolisation within 48 h of the procedure [223]. Although percutaneous vertebroplasty is usually safe, symptomatic pulmonary embolisation of acrylic cement used during this procedure has been described (fig. 5) [224].

Prostate brachytherapy, achieved by image-guided placement of radioactive seed implants carrying iodine-125 or palladium-103 in the prostate and periprostatic tissues, is a therapeutic option for patients with localised prostate cancer. These implants may detach from their insertion sites and migrate through the prominent periglandular or haemorrhoidal venous plexus to reach the pulmonary circulation [225]. The frequency of seed implant migration ranges from 0.7–55% [226], with an average of 2.2 embolised seeds per patient. Proper identification of periprostatic vessels and the use of individualised applicators have lowered the incidence of seed embolisation [227].

Pathophysiology

Talcum-induced pulmonary granulomatosis has an unknown physiopathological mechanism, although the most likely hypothesis is an immunological mechanism of delayed hypersensitivity. When medications are injected [228], the insoluble particles, such as microcrystalline cellulose and talcum, become trapped in the pulmonary arterioles causing both thrombosis and inflammation. Over time, these particles can penetrate the arteriolar wall and provoke a giant cell granulomatous reaction. In animals, cotton fibres disrupt the PA wall, with further passage of the cotton fibres into the alveoli and interstitium [229]. Within days after embolisation of cyano-acrylate, foci of medial and intimal necrosis have also been found in animal models [222]. Confluence of the granulomas, subsequent fibrosis and distortion of the lung architecture, especially in the upper lobes, may occur.

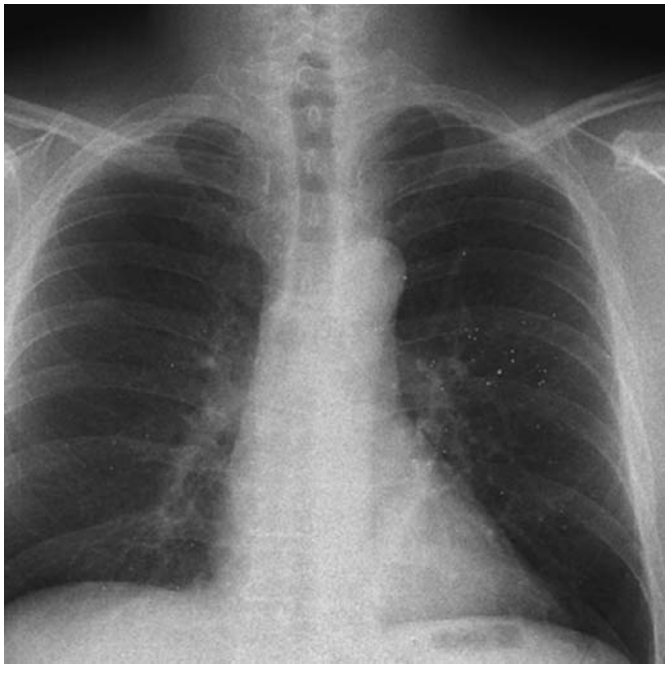

FIGURE 4. Chest radiograph of a male who presented at the emergency room after the intravenous injection of mercury during a suicide attempt. Note the small metallic spherules scattered throughout both lungs. Recognition of metallic opacities in the heart allows differentiation from aspiration.

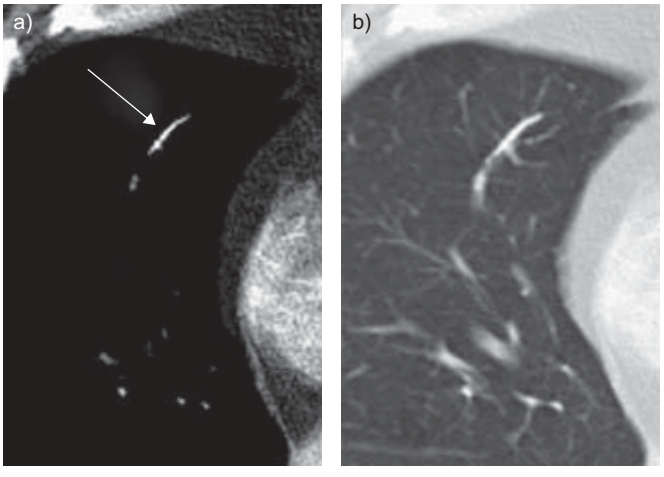

FIGURE 5. Polymethylmethacrylate embolism as an incidental finding after a history of percutaneous vertebroplasty. Axial computed tomography of a) the mediastinal and b) the pulmonary window shows a linear hyperdensity in a pulmonary artery branch (white arrow).

Pulmonary hypertension may develop as a result of chronic changes [230].

Birefringent material, such as that seen in talcum PE, is often but not exclusively demonstrated intracellularly in lung tissue (94%); this preferential pulmonary localisation is followed by the spleen, liver, lymph nodes and bone marrow. However, a granulomatous reaction was only observed in the lungs. Talcum was the only foreign material seen in organs other than the lungs, undoubtedly due to its smaller size [215]. Intrapulmonary crospovidone embolism exhibits degenerative changes, contributing to vascular injury by causing angiothrombosis and granulomatous angiitis [216]. In a consecutive series of 43 patients whose surgical lung biopsy demonstrated pulmonary infarction, embolotherapy and catheter embolism were observed in 2% of all cases [231].

Clinical signs

Most patients with talcum emboli are asymptomatic, although slowly progressive dyspnoea, persistent cough, nonspecific chest pain and occasionally anorexia, weight loss, fever and night sweats may occur. Lung sounds are usually normal or with minimal bibasal crepitations, and talcum deposits may be visualised in the retinal blood vessels [232]. Clinical features appear to be dose-related and may progress even after drug injections have been stopped [2, 230]. Multiple episodes of injection may thus elicit intractable pulmonary hypertension and death. Clinical symptoms associated with cellulose granulomatosis are also largely dependent on the extent of arteriolar involvement. Symptoms may range from none to exertional dyspnoea to sudden death [228]. Two out of 47 children undergoing therapeutic embolisation of cerebral arteriovenous malformation developed severe respiratory distress that required endotracheal intubation [222]. The clinical findings described in silicone embolism syndrome are very similar to those observed in FES. Dyspnoea, hypoxaemia, haemoptysis, alveolar haemorrhage, petechiae and altered consciousness were observed in a high percentage of these patients [221]. A mortality of as high as 24% has been reported [221]. Retained catheter fragments have been associated with an alarmingly high rate of complications [233]: a 45–71% incidence of serious consequences [233, 234] such as arrhythmias, perforation, infection and thrombus formation were observed days to even weeks after embolisation. Embolisation of periprostatic seed implants after brachytherapy may be underestimated by the lack of induced symptoms [225] and they usually migrate after the day of implantation [235].

Diagnosis

Respiratory function tests generally show a persistent slight-to-moderate hypoxaemia and a reduction of carbon monoxide diffusion. Initially, imaging reveals several small (1-mm) nodular and reticular opacities or interstitial nodules, some of which occur in a centrilobular distribution throughout the lungs after talcum or cellulose granulomatosis [236]. Later, homogeneous upper lobe opacities resembling massive fibrosis may be identified. Large pulmonary arteries and a large right heart may be observed in patients with pulmonary hypertension. Lymphadenopathy is rare [237]. Gallium lung scans generally show diffuse bilateral uptake in talcum granulomatosis. BAL typically reveals lymphocytosis with a predominance of CD8 lymphocytes, and talcum crystals can occasionally be seen [238]. Cellulose granulomatosis has also been described as a cause of the tree-in-bud appearance on high-resolution CT: micronodules distributed at the termination of bronchovascular bundles [160, 228]. These micronodules represent intra-arteriolar accumulation of microcrystalline cellulose with adjacent granulomatous reaction. In mercury embolism, chest radiographic findings are striking: multiple small metallic spherules either distributed diffusely throughout the lungs or occasionally restricted to one or more dependent areas (fig. 4). The opacities may be scattered or of different sizes or may appear as beaded chains simulating the appearance of an angiogram [220]. The radiographic abnormalities may be permanent or may resolve gradually [220]. In catheter emboli, radiographs may reveal a disconnected catheter fragment overlying an unexpected portion of the lung, mediastinum or heart. Generally, the course of the catheter corresponds to the expected location of the PA. Angiography or CT findings can obviously confirm the position of the catheter [2].

Definitive diagnosis requires histological examination of pulmonary tissue and is often only achieved at autopsy [212]. With time, aspirated material is often incorporated into alveolar septae, at which stage it can be difficult to distinguish from organising microembolic intravascular material. A definitive diagnosis is obtained by examining transbronchial or open-lung biopsy specimens, which generally show macrophages with intracellular talc crystals. Microembolic foreign material generally elicits a granulomatous reaction [212]. Identification of the particulates may require the use of ultrastructural analysis by analytical electron microscopy techniques, including selected area diffraction and X-ray energy-dispersive analysis [213]. Polarisation microscopy is an ideal means of detecting foreign material such as intravascular deposits and aspirated foreign matter. Talc is distinguished readily by its appearance under polarised light: it exhibits a birefringent appearance with sharp, elongate fibres. Talcum does not stain with Periodic Acid Schiff (PAS), silver or Congo red [215]. Cellulose particles are longer, mod-shaped, birefringent material [212]. Crospovidone appears as basophilic, coral-like particles within arteries and extravascular granulomas [216]. Organic starch has Maltese-cross morphology and stains positively with PAS [215]. A collimated gamma scintillation survey meter may be used to detect iodine-125 seeds after prostate brachytherapy, as their small size means the seeds are frequently neglected on a radiograph [239].

Treatment

The prognosis for patients with mercury emboli is reported as good, although death has been reported [3]. After several weeks, symptoms and functional impairments will diminish [240]. Given the high complication rate associated with embolic catheter fragments, efforts should be made to recover foreign bodies prior to central embolisation [218]. Many nonsurgical techniques have been developed to remove catheter material from the vessels, with a low complication rate [234]. Talcum granulomatosis and embolisation of other foreign materials may develop into pulmonary hypertension and fibrosis. Treatment with corticosteroids has been attempted, with gradual or temporary improvement, although there is a risk of relapse after cessation [241]. A number of patients with pulmonary disease due to injection of oral medications have undergone

lung transplantation [242]. However, recurrent and ongoing *i.v.* drug abuse, leading to a histiocytic reaction in the transplanted lung, should raise substantial concerns on performing lung transplantation in cases of substance abuse [242].

GAS EMBOLISM

The entry of gas into vessels was first described by Morgagni, whose post-mortem findings were published in 1769 [243, 244]. The first clinical report dates to 1821 [244]. Gas embolism (GE) is mainly air embolism (AE), although the use of other gases used in medical procedures or diving, such as carbon dioxide, nitrous oxide, nitrogen and helium, can also provoke these symptoms [245].

Incidence

The two different subtypes of GE, venous and arterial, can be distinguished by the mechanism of entry and the site where the emboli finally lodge. Preconditions for venous AE include a hydrostatic gradient favouring the intravascular entry of air and incising of noncollapsed veins: the epiploic and emissary veins, veins of the throat and dural venous sinuses in patients undergoing craniotomy in the sitting position [246]. It may enter the veins of the myometrium [247] during surgical or diagnostic gynaecological procedures [248]. The incidence of AE during surgery, as assessed by precordial Doppler, ranges from 7–69% [249].

Venous AE is often an iatrogenic problem during the manipulation of a central venous and haemodialysis catheter [250]: the incidence ranges 1 in 47–3000, with a mortality rate even reaching 30% [251]. It has been occasionally reported when a peripheral venous infusion was started [252] or after contrast-enhanced CT examination [253]. The incidences during diagnostic cardiac catheterisation and percutaneous coronary intervention are 0.84% and 0.24%, respectively [254]. AE is a rare complication of ventricular assist device pump dissection [255], ventilation-induced lung trauma [256] and laparoscopy which can lead to air, argon or carbon dioxide embolism [257, 258], Other causes include fibrinolytic pleural lavage [259], the intraoperative use of hydrogen peroxide, insufflation of air during endoscopy, laser therapy, arthroscopy, thoracotomy, noninvasive ventilation, carotid endarteriectomy or prostatectomy [245, 260].

The entry of gas into the pulmonary veins or the systemic arteries as a result of overexpansion of the lung by decompression barotrauma or a paradoxical embolism causes arterial embolism. Microbubbles, originating in extracorporeal devices but endogenous in cases of decompression sickness or mechanical heart valves, may cause arterial GE [261, 262].

Pathophysiology

Insidious venous AE causes a ''string'' of bubbles to enter the veins. Pulmonary vessel filtration protects the systemic and coronary circulation from AE orginating in the venous circulation [263]. When air bubbles are finally trapped in the pulmonary capillaries, the pulmonary arterial pressure increases, and the increased resistance to right ventricular outflow diminishes pulmonary venous return resulting in diminished cardiac output [264]. When >50 mL of gas is injected abruptly into human veins, acute cor pulmonale, asystoly or both can occur [265]. The lethal volume of injected air in humans is estimated to range 100–500 mL [2].

The entry into the bloodstream requires a pressure gradient: when venous pressure is negative as during spontaneous inspiration, gas is forced under pressure [266]; or when the vein is located higher than the heart [249]. The alteration in the resistance of the lung vessels and the mismatch between ventilation and perfusion cause intrapulmonary right-to-left shunting and increased alveolar dead space leading to decreased gas exchange [267], arrhythmia [268], pulmonary hypertension [268], right ventricular strain [269] and arterial AE related to shunting [270].

Bubbles in vessels can be absorbed and adhere [271]. Activated neutrophils sequestered in the pulmonary capillaries aggregate around the bubble [261]. Prostaglandins are realised increasing permeability, causing lung oedema [272] and inactivation of surfactant with alveolar collapse and atelectasis [273]. Impeded lymph flow by increased venous pressure further enhances lung oedema [274]. AE during diving is the clinical manifestation of Boyle's law as the result of overdistention of the alveoli by expanding gases during ascent [244]. A change in pressure of 70 mmHg, correlating with a full inspiration with compressed air at only 1 m under water, can cause barotrauma [275]. Air bubbles entering *via* a catheter may even rise retrograde against the flow to the brain [276].

Arterial GE causes ischaemia. Two mechanisms for AE after lung surgery were historically recognised: infusion of air into the pulmonary vein and arterialisation of venous bubbles via a foramen ovale [277]. Gas entry into the aorta obviously distributes bubbles into many organs. Small emboli in the vessels of skeletal muscles or viscera are tolerated, but hypoxaemia caused by obstruction of the coronary or cerebral arteries (cerebral arterial gas embolism (CAE)) may lead to fatality [245]. Intracoronary injection of a bolus of air leads to depression of heart function [278]. When bubbles occlude the brain vasculature, intracranial pressure (ICP) increases and ischaemia occurs [279]. Microbubbles ''irritate'' the cerebral vascular wall, leading to a breakdown of the blood–brain barrier [280]. Such tiny bubbles may briefly interrupt cerebral arteriolar flow [281]. Normalisation is often only temporary, and blood flow may subsequently decrease to levels below those required to maintain neuronal function [282]. Additionally, the contact of bubbles with the endothelium leads to activation of leukocytes in the damaged brain area [283]. The coagulation system, complement and kinines, are activated by bubbles [284] but coagulopathies, common in animal models, are rarely observed in humans [244].

A paradoxical embolism occurs when gas in the veins manages to enter the systemic arterial circulation. This may be caused by passage across a patent foramen ovale, rendering right-to-left shunting of gas bubbles feasible [285]. Elevated pulmonary arterial pressure due to venous GE may also result in elevated right atrial pressure, making it possible for a bubble to be transported through a patent foramen. Moreover, the decrease in left atrial pressure caused by ventilation, and the use of positive end-expiratory pressure may create a pressure gradient [265]. Venous gas may also enter the arterial circulation by overwhelming the mechanisms that prevent

arterial AE. This explains why CAE caused by a venous gas embolus has been described, although no intracardiac defects could be demonstrated [286]. Various volatile anaesthetic agents diminish the ability of the pulmonary circulation to filter out gas [287].

Clinical signs

In venous GE, manifestations include cough, dyspnoea, tachypnoea and a hypoxaemic ''gasp'' reflex when 10% of the pulmonary vessels are occluded [249, 266]. Arterial embolisation into the coronary arteries induces a specific drum-like or ''mill-wheel'' murmur and electrocardiographic changes of ischaemia [2]. Arrhythmias, cardiac failure and arrest are all possible [288]. Circulatory responses may also develop suddenly with embolisation to cerebral vessels [268]. The absolute quantity of gas and the areas of the brain that are affected determine the variety of symptoms: haemiparesis, paresthesias, paralysis, seizures, visual disturbances and headache [244, 289]. About 50% of patients will also have some history of (transitional) impaired unconsciousness [290]. Asymmetry of the pupils, haemianopsia and impairment of the respiratory and circulatory centres (manifested as Cheyne–Stokes breathing) [268, 288] are other well-known complications. A delayed recovery from general anaesthesia may help detect CAE. Detection of air in retinal vessels and the occurrence of sharply-defined areas of pallor on the tongue have been described. Marbling of the skin may occur and is especially noted in superiorly located body parts because the distribution of air is determined by the principle of air buoyancy [264].

Diagnosis

The real diagnostic criterion is the patient's history. In venous embolism, the mill-wheel murmur, a splashing auscultatory sound caused by the presence of gas in the cardiac chambers and great vessels, can be auscultated. Chest radiograph findings include normal findings, radiolucency in the PA, heart and hepatic veins, pulmonary oedema, enlarged central pulmonary arteries, dilatation of the superior vena cava and atelectasis [2]. Air in the distal PA may appear in a bell shape, and CT may reveal air in the veins, right heart or PA (fig. 6) [2]. A decrease in end-tidal carbon dioxide ($ETCO_2$) levels, as determined by capnometry [291], suggests a change in the relationship between ventilation and perfusion. $ETCO_2$ is the intraoperative standard and the magnitude and duration of $ETCO_2$ decrease correlate with the volume of embolised air [249]. Arterial saturation as measured by pulse oximetry is not able to detect AE as readily [292]. Precordial Doppler ultrasonography is a sensitive means of detecting intracardiac air, often used during surgical procedures [249, 293]. An even more sensitive method is echocardiography, which may detect air bubbles as small as 5 μm as white reflections and a patent foramen ovale [246]. Intracardiac transvenous echocardiography was superior to other techniques for detecting venous embolism in a swine model [294]. Gas bubbles in the retinal vessels can be identified. Another finding is haemoconcentration, possibly as a consequence of the extravascular shift of fluid into injured tissues [295].

CAE can sometimes be seen on CT [296] but in divers with neurological symptoms, CT was unable to show any evidence of CAE [297]. Abnormalities on brain MRI may range from no abnormalities up to local oedema, caused by an increased volume of water or hyperintense acute infarctions on diffusion weighted images [298]. As no imaging technique alone has sufficient accuracy to warrant its use for diagnostic purposes, diagnosis should be made on clinical suspicion without reliance on imaging [244].

Treatment

Aggressive treatment is essential. For venous GE, the mainstays of treatment are the prevention of further entry of gas, volume expansion, administration of 100% oxygen and cardiopulmonary resuscitation, if necessary. The patient should be placed in the left lateral decubitus position to prevent right ventricular outflow obstruction by airlock [251]. In a somnolent patient, resuscitation and intubation should be performed to maintain oxygenation [290]. Bilateral manual jugular venous compression can elevate the cerebral venous pressure for embolism during intracranial procedures [299]. Administration of up to 100% oxygen can decrease bubble size by establishing a diffusion gradient that favours the elimination of gas from the bubbles and by increasing the gradient for the egress of nitrogen from the bubbles [245, 300]. Attempting to evacuate air from the right ventricle with the use of a multiorifice central venous or pulmonary arterial catheter is recommended. Occasionally removal of up to 50% of the entrained gas can be achieved, with optimal placement of the catheter tip 2 cm below the junction of the superior vena cava and the right atrium [251, 265, 301].

Patients with arterial GE should be placed in the flat supine position. The buoyancy of gas bubbles is not sufficient to counteract blood flow, propelling such bubbles towards the head even when the patient is in a head-down position. In addition, the head-down position may aggravate cerebral oedema [302]. A short period of hypertension that occurs following bubble lodging in the cerebral circulation is therapeutic because it facilitates bubble redistribution to the

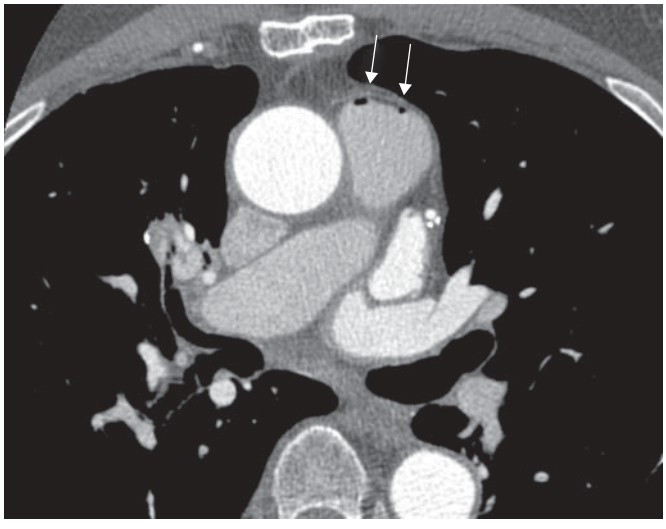

FIGURE 6. Incidentally found air-emboli on cardiac computed tomography (CT) in an asymptomatic 62-yr-old male. Axial contrast-enhanced CT image shows multiple small air bubbles in the main pulmonary artery (arrows).

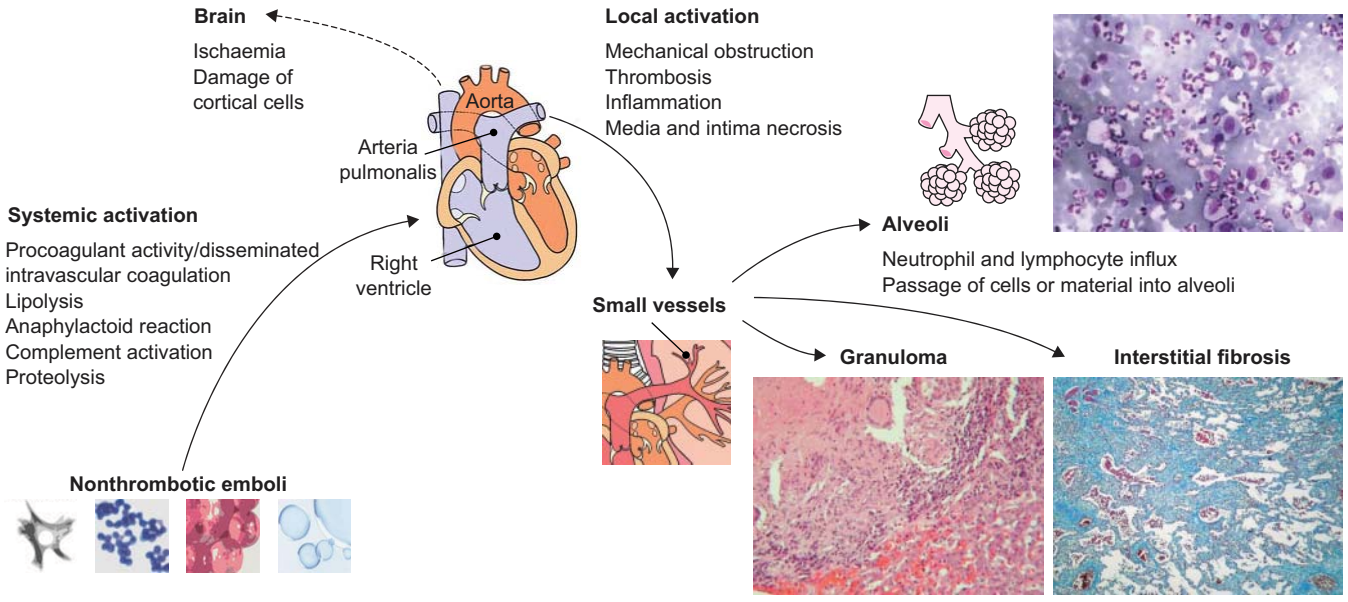

FIGURE 7. Different cell types (adipocyte, haematopoietic, amniotic, trophoblastic or tumour), bacteria, fungi, foreign material and gas may be carried in the blood stream and embolise to the pulmonary circulation. The complex and diverse pathogenesis of different subtypes of emboli is subject to continuing speculation and is certainly far more complex than ''simple'' mechanical obstruction after embolisation of vascular thrombi. Nonthrombotic emboli may also lead to a severe inflammatory reaction both in the systemic and pulmonary circulation, as well as in the lung. Acute and chronic nonthrombotic pulmonary embolism are an underestimated cause of acute and chronic pulmonary hypertension.

capillaries and veins [268]. The treatment goal is to maintain at least normal blood pressure and to prevent hypotension [245]. Seizures should be suppressed with barbiturates [289], thereby reducing cerebral oxygen consumption [303]. For arterial GE, hyperbaric oxygen (HBO) is the treatment of choice as soon as stabilisation has been achieved. The patient breathes 100% oxygen at a pressure above that of the atmosphere at sea level, decreasing the size of the gas bubbles by increasing the ambient pressure. The hyperoxia produces diffusion gradients for oxygen into and for nitrogen out of the bubble [302]. HBO decreases cerebral oedema, allows better oxygenation of already ischaemic tissue and diminishes the activation of leukocytes [289, 304, 305]. Although recovery rates vary widely, early application of HBO plays an important role in the management of CAE: a significantly better outcome in patients with venous AE with a delay in treatment of less than 6 hours was reported [290]. However, delayed treatment (up to 48 hours) may still ameliorate the patient's condition [306, 307].

As haemoconcentration leads to an increase in blood viscosity [295, 308], normovolemia should be achieved to optimise the microcirculation and to reduce neurological damage [309]. Colloid solutions are preferable because crystalloid solutions may promote cerebral oedema. The use of corticosteroids in patients with arterial GE is even more controversial. CAE induces swelling of cells (''cytotoxic oedema'') [310], a type of ischaemic injury aggravated by corticosteroids [311]. Animal studies suggest that lidocaine may be beneficial by preserving cerebral blood flow [244] and reducing ICP [245]. In one clinical trial, lidocaine provided cerebral protection during cardiac surgery [312]. The intravenous administration of fluorocarbons, characterised by high gas-dissolving capacity and low viscosity [313], should increase tissue oxygen delivery and shrink gas bubbles because of higher diffusion gradient. Animal studies demonstrated an improvement in cardiovascular function after AE [244], but more studies are needed to prove their efficacy in humans [314]. Nitric oxide (NO) might be involved in the prevention of bubble formation, the central goal in decompression procedures. The intake of an NO donor reduces bubble formation following decompression in divers [315].

CONCLUSION

Adipocytes, as well as haematopoietic, amniotic, trophoblastic or tumour cells, can embolise to the lung. This list may be extended to bacteria, fungi, foreign material and gas. This diversity of emboli causes a wide variety of clinical signs also related to a complex and diverse pathogenesis. Far more complex than the ''simple'' mechanical obstruction after embolisation of vascular thrombi, nonthrombotic emboli may additionally lead to severe inflammatory reactions both in the systemic and the pulmonary circulation (fig. 7). NTPE presents a formidable diagnostic challenge because the condition often presents with very unusual and peculiar clinical signs that are frequently overlooked. They range from very dramatic hyperacute presentations, such as ARDS in fat and AE, or signs observed late in the disease course, such as in tumour emboli. Pathological observations play a key role in the exact diagnosis, as sometimes carefully aspirated blood from the PA or specific staining of cells recovered from BAL fluid may be helpful in the diagnosis. Frequently, lung biopsies revealing the severe granulomatous reaction or unfortunate *post-mortem* pathological investigations of pulmonary tissue are necessary to confirm the diagnosis. On thin-section CT of the lungs, peculiar radiographic findings such a feeding vessel, the tree-in-bud pattern

or the appearance of micronodules distributed at the termination of bronchovascular bundles may be seen in certain forms. From this review, we also hope to increase the awareness of acute and chronic NTPE as an underestimated cause of acute and chronic pulmonary hypertension. Despite the detailed descriptions of several forms of NTPE available for almost 100 years, well-designed trials have never been performed to evaluate therapy in the different subsets of these patients.

STATEMENT OF INTEREST

None declared.

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REFERENCES

1 Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999; 353: 1386–1389.
2 Rossi SE, Goodman PC, Franquet T. Nonthrombotic pulmonary emboli. *AJR Am J Roentgenol* 2000; 174: 1499–1508.
3 Han D, Lee KS, Franquet T, *et al.* Thrombotic and nonthrombotic pulmonary arterial embolism: spectrum of imaging findings. *Radiographics* 2003; 23: 1521–1539.
4 Zenker FA. Beitrage zur normalen und pathologischen Anatomie der Lunge. Dresden, Schoenfeld, 1861.
5 Parisi DM, Koval K, Egol K. Fat embolism syndrome. *Am J Orthop* 2002; 31: 507–512.
6 Koessler MJ, Fabiani R, Hamer H, *et al.* The clinical relevance of embolic events detected by transesophageal echocardiography during cemented total hip arthroplasty: a randomized clinical trial. *Anesth Analg* 2001; 92: 49–55.
7 Richards RR. Fat embolism syndrome. *Can J Surg* 1997; 40: 334–339.
8 Muller C, Rahn BA, Pfister U, *et al.* The incidence, pathogenesis, diagnosis, and treatment of fat embolism. *Orthop Rev* 1994; 23: 107–117.
9 Peltier LF. Fat embolism. A current concept. *Clin Orthop Relat Res* 1969; 66: 241–253.
10 Robert JH, Hoffmeyer P, Broquet PE, *et al.* Fat embolism syndrome. *Orthop Rev* 1993; 22: 567–571.
11 Kontakis GM, Tossounidis T, Weiss K, *et al.* Fat embolism: special situations bilateral femoral fractures and pathologic femoral fractures. *Injury* 2006; 37: Suppl. 4, S19–S24.
12 Riska EB, von Bonsdorff H, Hakkinen S, *et al.* Primary operative fixation of long bone fractures in patients with multiple injuries. *J Trauma* 1977; 17: 111–121.
13 Tsokos M, Paulsen F, Petri S, *et al.* Histologic, immunohistochemical, and ultrastructural findings in human blast lung injury. *Am J Respir Crit Care Med* 2003; 168: 549–555.
14 Mudd KL, Hunt A, Matherly RC, *et al.* Analysis of pulmonary fat embolism in blunt force fatalities. *J Trauma* 2000; 48: 711–715.
15 Buchanan D, Mason JK. Occurrence of pulmonary fat and bone marrow embolism. *Am J Forensic Med Pathol* 1982; 3: 73–78.
16 Vichinsky EP, Neumayr LD, Earles AN, *et al.* Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med* 2000; 342: 1855–1865.
17 Hasan MY, Kissoon N, Khan TM, *et al.* Intraosseous infusion and pulmonary fat embolism. *Pediatr Crit Care Med* 2001; 2: 133–138.
18 Baselga J, Reich L, Doherty M, *et al.* Fat embolism syndrome following bone marrow harvesting. *Bone Marrow Transplant* 1991; 7: 485–486.
19 Graham JK, Mosunjac M, Hanzlick RL, *et al.* Sickle cell lung disease and sudden death: a retrospective/prospective study of 21 autopsy cases and literature review. *Am J Forensic Med Pathol* 2007; 28: 168–172.
20 Currie I, Drutz HP, Deck J, *et al.* Adipose tissue and lipid droplet embolism following periurethral injection of autologous fat: case report and review of the literature. *Int Urogynecol J Pelvic Floor Dysfunct* 1997; 8: 377–380.
21 Schulz F, Trubner K, Hildebrand E. Fatal fat embolism in acute hepatic necrosis with associated fatty liver. *Am J Forensic Med Pathol* 1996; 17: 264–268.
22 Guardia SN, Bilbao JM, Murray D, *et al.* Fat embolism in acute pancreatitis. *Arch Pathol Lab Med* 1989; 113: 503–506.
23 Platt MS, Kohler LJ, Ruiz R, *et al.* Deaths associated with liposuction: case reports and review of the literature. *J Forensic Sci* 2002; 47: 205–207.
24 Kitchell CC, Balogh K. Pulmonary lipid emboli in association with long-term hyperalimentation. *Hum Pathol* 1986; 17: 83–85.
25 Tolentino LF, Tsai SF, Witt MD, *et al.* Fatal fat embolism following amphotericin B lipid complex injection. *Exp Mol Pathol* 2004; 77: 246–248.
26 Francis RA, Barnes PA, Libshitz HI. Pulmonary oil embolism after lymphangiography. *J Comput Assist Tomogr* 1983; 7: 170–171.
27 Hejka AG, Poquette M, Wiebe DA, *et al.* Fatal intravenous injection of monooctanoin. *Am J Forensic Med Pathol* 1990; 11: 165–170.
28 Seifert SA, Dart RC, Kaplan EH. Accidental, intravenous infusion of a peanut oil-based medication. *J Toxicol* 1998; 36: 733–736.
29 Rabah R, Evans RW, Yunis EJ. Mineral oil embolization and lipid pneumonia in an infant treated for Hirschsprung's disease. *Pediatr Pathol* 1987; 7: 447–455.
30 Kiyokawa H, Utsumi K, Minemura K, *et al.* Fat embolism syndrome caused by vegetable oil injection. *Intern Med* 1995; 34: 380–383.
31 Bierre AR, Koelmeyer TD. Pulmonary fat and bone marrow embolism in aircraft accident victims. *Pathology* 1983; 15: 131–135.
32 Kerstell J. Pathogenesis of post-traumatic fat embolism. *Am J Surg* 1971; 121: 712–715.
33 Giannoudis PV, Tzioupis C, Pape HC. Fat embolism: the reaming controversy. *Injury* 2006; 37: Suppl. 4, S50–S58.
34 Schult M, Kuchle R, Hofmann A, *et al.* Pathophysiological advantages of rinsing-suction-reaming (RSR) in a pig model for intramedullary nailing. *J Orthop Res* 2006; 24: 1186–1192.
35 Kropfl A, Davies J, Berger U, *et al.* Intramedullary pressure and bone marrow fat extravasation in reamed and unreamed femoral nailing. *J Orthop Res* 1999; 17: 261–268.
36 Ott MC, Meschia JF, Mackey DC, *et al.* Cerebral embolization presenting as delayed, severe obtundation in the postanesthesia care unit after total hip arthroplasty. *Mayo Clin Proc* 2000; 75: 1209–1213.
37 Edmonds CR, Barbut D, Hager D, *et al.* Intraoperative cerebral arterial embolization during total hip arthroplasty. *Anesthesiology* 2000; 93: 315–318.
38 Baker PL, Pazell JA, Peltier LF. Free fatty acids, catecholamines, and arterial hypoxia in patients with fat embolism. *J Trauma* 1971; 11: 1026–1030.
39 Styles LA, Schalkwijk CG, Aarsman AJ, *et al.* Phospholipase A2 levels in acute chest syndrome of sickle cell disease. *Blood* 1996; 87: 2573–2578.
40 Hulman G. Fat macroglobule formation from chylomicrons and non-traumatic fat embolism. *Clin Chim Acta* 1988; 177: 173–178.
41 Mastrangelo AM, Jeitner TM, Eaton JW. Oleic acid increases cell surface expression and activity of CD11b on human neutrophils. *J Immunol* 1998; 161: 4268–4275.

42 Gurd AR. Fat embolism: an aid to diagnosis. *J Bone Joint Surg Br* 1970; 52: 732–737.
43 Gurd AR, Wilson RI. The fat embolism syndrome. *J Bone Joint Surg Br* 1974; 56B: 408–416.
44 Beck JP, Collins JA. Theoretical and clinical aspects of posttraumatic fat embolism syndrome. *AAOS Instr Course Lect*, 1973: 38–44.
45 Bulger EM, Smith DG, Maier RV, *et al.* Fat embolism syndrome. A 10-year review. *Arch Surg* 1997; 132: 435–439.
46 Bernard GR, Artigas A, Brigham KL, *et al.* The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149: 818–824.
47 Font MO, Nadal P, Bertran A. Fat embolism syndrome with no evidence of pulmonary involvement. *Crit Care Med* 1989; 17: 108–109.
48 Parizel PM, Demey HE, Veeckmans G, *et al.* Early diagnosis of cerebral fat embolism syndrome by diffusion-weighted MRI (starfield pattern). *Stroke* 2001; 32: 2942–2944.
49 Kearns TP. Fat embolism of the retina demonstrated by a flat retinal preparation. *Am J Ophthalmol* 1956; 41: 1–2.
50 Van den Brande FG, Hellemans S, De Schepper A, *et al.* Posttraumatic severe fat embolism syndrome with uncommon CT findings. *Anaesth Intensive Care* 2006; 34: 102–106.
51 Huybrechts W, Jorens PG, Jacquemyn Y, *et al.* Amniotic fluid embolism: a rare cause of acute left-sided heart failure. *Acta Cardiol* 2006; 61: 643–649.
52 Pluymakers C, De Weerdt A, Jacquemyn Y, *et al.* Amniotic fluid embolism after surgical trauma: two case reports and review of the literature. *Resuscitation* 2007; 72: 324–332.
53 Castella X, Valles J, Cabezuelo MA, *et al.* Fat embolism syndrome and pulmonary microvascular cytology. *Chest* 1992; 101: 1710–1711.
54 Gitin TA, Seidel T, Cera PJ, *et al.* Pulmonary microvascular fat: the significance? *Crit Care Med* 1993; 21: 673–677.
55 Puntis JW, Rushton DI. Pulmonary intravascular lipid in neonatal necropsy specimens. *Arch Dis Child* 1991; 66: 26–28.
56 Lechapt E, Habibi A, Bachir D, *et al.* Induced sputum *versus* bronchoalveolar lavage during acute chest syndrome in sickle cell disease. *Am J Respir Crit Care Med* 2003; 168: 1373–1377.
57 Roger N, Xaubet A, Agusti C, *et al.* Role of bronchoalveolar lavage in the diagnosis of fat embolism syndrome. *Eur Respir J* 1995; 8: 1275–1280.
58 Godeau B, Schaeffer A, Bachir D, *et al.* Bronchoalveolar lavage in adult sickle cell patients with acute chest syndrome: value for diagnostic assessment of fat embolism. *Am J Respir Crit Care Med* 1996; 153: 1691–1696.
59 Chastre J, Fagon JY, Soler P, *et al.* Bronchoalveolar lavage for rapid diagnosis of the fat embolism syndrome in trauma patients. *Ann Intern Med* 1990; 113: 583–588.
60 Mimoz O, Edouard A, Beydon L, *et al.* Contribution of bronchoalveolar lavage to the diagnosis of posttraumatic pulmonary fat embolism. *Intensive Care Med* 1995; 21: 973–980.
61 Benzer A, Ofner D, Totsch M, *et al.* Early diagnosis of fat embolism syndrome by automated image analysis of alveolar macrophages. *J Clin Monit* 1994; 10: 213–215.
62 Turillazzi E, Riezzo I, Neri M, *et al.* The diagnosis of fatal pulmonary fat embolism using quantitative morphometry and confocal laser scanning microscopy. *Pathol Res Pract* 2008; 204: 259–266.
63 Karagiorga G, Nakos G, Galiatsou E, *et al.* Biochemical parameters of bronchoalveolar lavage fluid in fat embolism. *Intensive Care Med* 2006; 32: 116–123.
64 Gallardo X, Castaner E, Mata JM, *et al.* Nodular pattern at lung computed tomography in fat embolism syndrome: a helpful finding. *J Comput Assist Tomogr* 2006; 30: 254–257.
65 Hamrick-Turner J, Abbitt PL, Harrison RB, *et al.* Diffuse lung calcifications following fat emboli and adult respiratory distress syndromes: CT findings. *J Thorac Imaging* 1994; 9: 47–50.
66 Hansell DM. Small-vessel diseases of the lung: CT-pathologic correlates. *Radiology* 2002; 225: 639–653.
67 Skarzynski JJ, Slavin JD Jr, Spencer RP, *et al.* ''Matching'' ventilation/perfusion images in fat embolization. *Clin Nucl Med* 1986; 11: 40–41.
68 Guillevin R, Vallee JN, Demeret S, *et al.* Cerebral fat embolism: usefulness of magnetic resonance spectroscopy. *Ann Neurol* 2005; 57: 434–439.
69 Takahashi M, Suzuki R, Osakabe Y, *et al.* Magnetic resonance imaging findings in cerebral fat embolism: correlation with clinical manifestations. *J Trauma* 1999; 46: 324–327.
70 Forteza AM, Koch S, Romano JG, *et al.* Transcranial doppler detection of fat emboli. *Stroke* 1999; 30: 2687–2691.
71 Brundage SI, McGhan R, Jurkovich GJ, *et al.* Timing of femur fracture fixation: effect on outcome in patients with thoracic and head injuries. *J Trauma* 2002; 52: 299–307.
72 Behrman SW, Fabian TC, Kudsk KA, *et al.* Improved outcome with femur fractures: early *vs*. delayed fixation. *J Trauma* 1990; 30: 792–797.
73 Bone LB, Johnson KD, Weigelt J, *et al.* Early *versus* delayed stabilization of femoral fractures. A prospective randomized study. *J Bone Joint Surg Am* 1989; 71: 336–340.
74 Rokkanen P, Alho A, Avikainen V, *et al.* The efficacy of corticosteroids in severe trauma. *Surg Gynecol Obstet* 1974; 138: 69–73.
75 Schonfeld SA, Ploysongsang Y, DiLisio R, *et al.* Fat embolism prophylaxis with corticosteroids. A prospective study in high-risk patients. *Ann Intern Med* 1983; 99: 438–443.
76 Liu DD, Kao SJ, Chen HI. N-acetylcysteine attenuates acute lung injury induced by fat embolism. *Crit Care Med* 2008; 36: 565–571.
77 Webb DP, McKamie WA, Pietsch JB. Resuscitation of fat embolism syndrome with extracorporeal membrane oxygenation. *J Extra Corpor Technol* 2004; 36: 368–370.
78 Forteza AM, Rabinstein A, Koch S, *et al.* Endovascular closure of a patent foramen ovale in the fat embolism syndrome: changes in the embolic patterns as detected by transcranial Doppler. *Arch Neurol* 2002; 59: 455–459.
79 Fletcher SJ, Parr MJ. Amniotic fluid embolism: a case report and review. *Resuscitation* 2000; 43: 141–146.
80 Steiner PE, Luschbaugh CC. Maternal pulmonary embolism by amniotic fluid as a cause of obstetric shock and unexpected deaths in obstetrics. *JAMA* 1941; 117: 1245–1254.
81 Morgan M. Amniotic fluid embolism. *Anaesthesia* 1979; 34: 20–32.
82 Davies MG, Harrison JC. Amniotic fluid embolism: maternal mortality revisited. *Br J Hosp Med* 1992; 47: 775–776.
83 Tuffnell DJ. United kingdom amniotic fluid embolism register. *BJOG* 2005; 112: 1625–1629.
84 Gilbert WM, Danielsen B. Amniotic fluid embolism: decreased mortality in a population-based study. *Obstet Gynecol* 1999; 93: 973–977.
85 Clark SL. New concepts of amniotic fluid embolism: a review. *Obstet Gynecol Surv* 1990; 45: 360–368.
86 Clark SL, Hankins GD, Dudley DA, *et al.* Amniotic fluid embolism: analysis of the national registry. *Am J Obstet Gynecol* 1995: 172: 1158–1167.
87 Devriendt J, Machayekhi S, Staroukine M. Amniotic fluid embolism: another case with non-cardiogenic pulmonary edema. *Intensive Care Med* 1995; 21: 698–699.
88 Hasaart TH, Essed GG. Amniotic fluid embolism after transabdominal amniocentesis. *Eur J Obstet Gynecol Reprod Biol* 1983; 16: 25–30.
89 Guidotti RJ, Grimes DA, Cates W Jr. Fatal amniotic fluid embolism during legally induced abortion, United States, 1972 to 1978. *Am J Obstet Gynecol* 1981; 141: 257–261.
90 Grimes DA, Schulz KF. Morbidity and mortality from second-trimester abortions. *J Reprod Med* 1985; 30: 505–514.

91 Laforga JB. Amniotic fluid embolism. Report of two cases with coagulation disorder. *Acta Obstet Gynecol Scand* 1997; 76: 805–806.
92 Grimes DA, Cates W Jr. Fatal amniotic fluid embolism during induced abortion, 1972–1975. *South Med J* 1977; 70: 1325–1326.
93 Margan I, Urbancic S, Voncina D, *et al.* [Amniotic fluid embolism in multiple pregnancy in the second trimester of gestation.]. *Jugosl Ginekol Opstet* 1984; 24: 29–32.
94 Olcott C 4th., Robinson AJ., Maxwell TM., Griffin HA., Amniotic fluid embolism and disseminated intravascular coagulation after blunt abdominal trauma. *J Trauma* 1973; 13: 737–740.
95 Maher JE, Wenstrom KD, Hauth JC, *et al.* Amniotic fluid embolism after saline amnioinfusion: two cases and review of the literature. *Obstet Gynecol* 1994; 83: 851–854.
96 Abenhaim HA, Azoulay L, Kramer MS, *et al.* Incidence and risk factors of amniotic fluid embolisms: a population-based study on 3 million births in the United States. *Am J Obstet Gynecol* 2008; 199: e1–e8.
97 Chang M, Herbert WN. Retinal arteriolar occlusions following amniotic fluid embolism. *Ophthalmology* 1984; 91: 1634–1637.
98 Liban E, Raz S. A clinicopathologic study of fourteen cases of amniotic fluid embolism. *Am J Clin Pathol* 1969; 51: 477–486.
99 Vedernikov YP, Saade GR, Zlatnik M, *et al.* The effect of amniotic fluid on the human omental artery in vitro. *Am J Obstet Gynecol* 1999; 180: 454–456.
100 Balazic J, Rott T, Jancigaj T, *et al.* Amniotic fluid embolism with involvement of the brain, lungs, adrenal glands, and heart. *Int J Legal Med* 2003; 117: 165–169.
101 Fineschi V, Gambassi R, Gherardi M, *et al.* The diagnosis of amniotic fluid embolism: an immunohistochemical study for the quantification of pulmonary mast cell tryptase. *Int J Legal Med* 1998; 111: 238–243.
102 Rainio J, Penttila A. Amniotic fluid embolism as cause of death in a car accident--a case report. *Forensic Sci Int* 2003; 137: 231–234.
103 Nishio H, Matsui K, Miyazaki T, *et al.* A fatal case of amniotic fluid embolism with elevation of serum mast cell tryptase. *Forensic Sci Int* 2002; 126: 53–56.
104 Benson MD, Kobayashi H, Silver RK, *et al.* Immunologic studies in presumed amniotic fluid embolism. *Obstet Gynecol* 2001; 97: 510–514.
105 Davies S. Amniotic fluid embolism and isolated disseminated intravascular coagulation. *Can J Anaesth* 1999; 46: 456–459.
106 Harnett MJ, Hepner DL, Datta S, *et al.* Effect of amniotic fluid on coagulation and platelet function in pregnancy: an evaluation using thromboelastography. *Anaesthesia* 2005; 60: 1068–1072.
107 Liu EH, Shailaja S, Koh, *et al.* An assessment of the effects on coagulation of midtrimester and final-trimester amniotic fluid on whole blood by Thrombelastograph analysis. *Anesth Analg* 2000; 90: 333–336.
108 Uszynski M, Zekanowska E, Uszynski W, *et al.* Tissue factor (TF) and tissue factor pathway inhibitor (TFPI) in amniotic fluid and blood plasma: implications for the mechanism of amniotic fluid embolism. *Eur J Obstet Gynecol Reprod Biol* 2001; 95: 163–166.
109 Richards DS, Carter LS, Corke B, *et al.* The effect of human amniotic fluid on the isolated perfused rat heart. *Am J Obstet Gynecol* 1988; 158: 210–214.
110 Vermeiren GL, Claeys MJ, Van Bockstaele D, *et al.* Reperfusion injury after focal myocardial ischaemia: polymorphonuclear leukocyte activation and its clinical implications. *Resuscitation* 2000; 45: 35–61.
111 Courtney LD. Amniotic fluid embolism. *Obstet Gynecol Surv* 1974; 29: 169–177.
112 Benson MD. A hypothesis regarding complement activation and amniotic fluid embolism. *Med Hypotheses* 2007; 68: 1019–1025.
113 Moore J, Baldisseri MR: Amniotic fluid embolism. *Crit Care Med* 2005; 33:10 Suppl, S279–S285.
114 Vanmaele L, Noppen M, Vincken W, *et al.* Transient left heart failure in amniotic fluid embolism. *Intensive Care Med* 1990; 16: 269–271.
115 Clark SL. Amniotic fluid embolism. *Clin Perinatol* 1986; 13: 801–811.
116 Giampaolo C, Schneider V, Kowalski BH, *et al.* The cytologic diagnosis of amniotic fluid embolism: a critical reappraisal. *Diagn Cytopathol* 1987; 3: 126–128.
117 Masson RG, Ruggieri J. Pulmonary microvascular cytology. A new diagnostic application of the pulmonary artery catheter. *Chest* 1985; 88: 908–914.
118 Masson RG. Amniotic fluid embolism. *Clin Chest Med* 1992; 13: 657–665.
119 Davies S. Amniotic fluid embolus: a review of the literature. *Can J Anaesth* 2001; 48: 88–98.
120 Lee KR, Catalano PM, Ortiz-Giroux S. Cytologic diagnosis of amniotic fluid embolism. Report of a case with a unique cytologic feature and emphasis on the difficulty of eliminating squamous contamination. *Acta Cytol* 1986; 30: 177–182.
121 Shapiro SH, Wessely Z. Rhodamine B fluorescence as a stain for amniotic fluid squames in maternal pulmonary embolism and fetal lungs. *Ann Clin Lab Sci* 1988; 18: 451–454.
122 Lunetta P, Penttila A. Immunohistochemical identification of syncytiotrophoblastic cells and megakaryocytes in pulmonary vessels in a fatal case of amniotic fluid embolism. *Int J Legal Med* 1996; 108: 210–214.
123 Ishiyama I, Mukaida M, Komuro E, *et al.* Analysis of a case of generalized amniotic fluid embolism by demonstrating the fetal isoantigen (A blood type) in maternal tissues of B blood type, using immunoperoxidase staining. *Am J Clin Pathol* 1986; 85: 239–241.
124 Oi H, Kobayashi H, Hirashima Y, *et al.* Serological and immunohistochemical diagnosis of amniotic fluid embolism. *Semin Thromb Hemost* 1998; 24: 479–484.
125 Kobayashi H, Ooi H, Hayakawa H, *et al.* Histological diagnosis of amniotic fluid embolism by monoclonal antibody TKH-2 that recognizes NeuAc alpha 2-6GalNAc epitope. *Hum Pathol* 1997; 28: 428–433.
126 Kanayama N, Yamazaki T, Naruse H, *et al.* Determining zinc coproporphyrin in maternal plasma–a new method for diagnosing amniotic fluid embolism. *Clin Chem* 1992; 38: 526–529.
127 Bauer P, Lelarge P, Hennequin L, *et al.* Thrombo-embolism during amniotic fluid embolism. *Intensive Care Med* 1995; 21: 384.
128 Alon E, Atanassoff PG. Successful cardiopulmonary resuscitation of a parturient with amniotic fluid embolism. *Int J Obstet Anesth* 1992; 1: 205–207.
129 Rodgers GP, Heymach GJ 3rd. Cryoprecipitate therapy in amniotic fluid embolization. *Am J Med* 1984; 76: 916–920.
130 Lim Y, Loo CC, Chia V, *et al.* Recombinant factor VIIa after amniotic fluid embolism and disseminated intravascular coagulopathy. *Int J Gynaecol Obstet* 2004; 87: 178–179.
131 Waters JH, Biscotti C, Potter PS, *et al.* Amniotic fluid removal during cell salvage in the cesarean section patient. *Anesthesiology* 2000; 92: 1531–1536.
132 Goldszmidt E, Davies S. Two cases of hemorrhage secondary to amniotic fluid embolus managed with uterine artery embolization. *Can J Anaesth* 2003; 50: 917–921.
133 Kaneko Y, Ogihara T, Tajima H, *et al.* Continuous hemodiafiltration for disseminated intravascular coagulation and shock due to amniotic fluid embolism: report of a dramatic response. *Intern Med* 2001; 40: 945–947.
134 McDonnell NJ, Chan BO, Frengley RW. Rapid reversal of critical haemodynamic compromise with nitric oxide in a parturient with amniotic fluid embolism. *Intern J Obstetr Anesthesia* 2007; 16: 269–273.
135 Van Heerden PV, Webb SA, Hee G, *et al.* Inhaled aerosolized prostacyclin as a selective pulmonary vasodilator for the

treatment of severe hypoxaemia. *Anaesth Intensive Care* 1996; 24: 87–90.
136 Hsieh YY, Chang CC, Li PC, *et al.* Successful application of extracorporeal membrane oxygenation and intra-aortic balloon counterpulsation as lifesaving therapy for a patient with amniotic fluid embolism. *Am J Obstet Gynecol* 2000; 183: 496–497.
137 Esposito RA, Grossi EA, Coppa G, *et al.* Successful treatment of postpartum shock caused by amniotic fluid embolism with cardiopulmonary bypass and pulmonary artery thromboembolectomy. *Am J Obstet Gynecol* 1990; 163: 572–574.
138 Schmidt MB. Die Verbreitungswege der Karcinome und die Beziehung Generalisierter Sarcoma zu den Leukämischen Neubildungen. Jena, G. Fischer, 1903.
139 Brill IC, Robertson TD. Subacute cor pulmonale. *Arch Intern Med* 1937; 60: 1043–1057.
140 Jakel J, Ramaswamy A, Kohler U, *et al.* Massive pulmonary tumor microembolism from a hepatocellular carcinoma. *Pathol Res Pract* 2006; 202: 395–399.
141 Chan CK, Hutcheon MA, Hyland RH, *et al.* Pulmonary tumor embolism: a critical review of clinical, imaging, and hemodynamic features. *J Thorac Imaging* 1987; 2: 4–14.
142 Montero A, Vidaller A, Mitjavila F, *et al.* Microscopic pulmonary tumoral embolism and subacute cor pulmonale as the first clinical signs of cancer. *Acta Oncol* 1999; 38: 1116–1118.
143 Sperling BL, Cockcroft DW, Chibbar R. Microscopic pulmonary tumour embolism: an unusual presentation of thymic carcinoma. *Can Respir J* 2002; 9: 347–350.
144 Seo JB, Im JG, Goo JM, *et al.* Atypical pulmonary metastases: spectrum of radiologic findings. *Radiographics* 2001; 21: 403–417.
145 Brock SJ, Fuller C, Iveson TJ. Pulmonary tumour emboli: a difficult ante-mortem diagnosis. *Clin Oncol (R Coll Radiol)* 2000; 12: 56–57.
146 Winterbauer RH, Elfenbein IB, Ball WC Jr. Incidence and clinical significance of tumor embolization to the lungs. *Am J Med* 1968; 45: 271–290.
147 Kane RD, Hawkins HK, Miller JA, *et al.* Microscopic pulmonary tumor emboli associated with dyspnea. *Cancer* 1975; 36: 1473–1482.
148 Veinot JP, Ford SE, Price RG. Subacute cor pulmonale due to tumor embolization. *Arch Pathol Lab Med* 1992; 116: 131–134.
149 Grass H, Schuff A, Staak M, *et al.* Tumor embolism as a cause of an unexpected death: a case report. *Pathol Res Pract* 2003; 199: 349–352.
150 Ishiguro T, Kasahara K, Matsumoto I, *et al.* Primary pulmonary artery sarcoma detected with a pulmonary infarction. *Intern Med* 2007; 46: 601–604.
151 Nakamura H, Adachi H, Sudoh A, *et al.* Subacute cor pulmonale due to tumor embolism. *Intern Med* 2004; 43: 420–422.
152 Chinen K, Kazumoto T, Ohkura Y, *et al.* Pulmonary tumor thrombotic microangiopathy caused by a gastric carcinoma expressing vascular endothelial growth factor and tissue factor. *Pathol Int* 2005; 55: 27–31.
153 Roberts KE, Hamele-Bena D, Saqi A, *et al.* Pulmonary tumor embolism: a review of the literature. *Am J Med* 2003; 115: 228–232.
154 Pinckard JK, Wick MR. Tumor-related thrombotic pulmonary microangiopathy: review of pathologic findings and pathophysiologic mechanisms. *Ann Diagn Pathol* 2000; 4: 154–157.
155 Shields DJ, Edwards WD. Pulmonary hypertension attributable to neoplastic emboli: an autopsy study of 20 cases and a review of the literature. *Cardiovasc Pathol* 1992; 1: 279–287.
156 Goldhaber SZ, Dricker E, Buring JE, *et al.* Clinical suspicion of autopsy-proven thrombotic and tumor pulmonary embolism in cancer patients. *Am Heart J* 1987; 114: 1432–1435.
157 Crane R, Rudd TG, Dail D. Tumor microembolism: pulmonary perfusion pattern. *J Nucl Med* 1984; 25: 877–880.
158 Shepard JA, Moore EH, Templeton PA, *et al.* Pulmonary intravascular tumor emboli: dilated and beaded peripheral pulmonary arteries at CT. *Radiology* 1993; 187: 797–801.
159 Schriner RW, Ryu JH, Edwards WD. Microscopic pulmonary tumor embolism causing subacute cor pulmonale: a difficult antemortem diagnosis. *Mayo Clin Proc* 1991; 66: 143–148.
160 Rossi SE, Franquet T, Volpacchio M, *et al.* Tree-in-bud pattern at thin-section CT of the lungs: radiologic-pathologic overview. *Radiographics* 2005; 25: 789–801.
161 Franquet T, Gimenez A, Prats R, *et al.* Thrombotic microangiopathy of pulmonary tumors: a vascular cause of tree-in-bud pattern on CT. *AJR Am J Roentgenol* 2002; 179: 897–899.
162 Masson RG, Krikorian J, Lukl P, *et al.* Pulmonary microvascular cytology in the diagnosis of lymphangitic carcinomatosis. *N Engl J Med* 1989; 321: 71–76.
163 Lurain JR. Gestational trophoblastic tumors. *Semin Surg Oncol* 1990; 6: 347–353.
164 Hankins GD, Wendel GD, Snyder RR, *et al.* Trophoblastic embolization during molar evacuation: central hemodynamic observations. *Obstet Gynecol* 1987; 69: 368–372.
165 Garner EI, Chang-Lee WY, Lu KH, *et al.* Trophoblastic pulmonary embolization after hysterectomy for invasive complete mole. A case report. *J Reprod Med* 1999; 44: 908–912.
166 Delmis J, Pfeifer D, Ivanisevic M, *et al.* Sudden death from trophoblastic embolism in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2000; 92: 225–227.
167 Smith JC, Alsuleiman SA, Bishop H, *et al.* Trophoblastic pulmonary embolism. *South Med J* 1981; 74: 916–919.
168 Twiggs LB, Morrow CP, Schlaerth JB. Acute pulmonary complications of molar pregnancy. *Am J Obstet Gynecol* 1979; 135: 189–194.
169 Coukos G, Makrigiannakis A, Chung J, *et al.* Complete hydatidiform mole. A disease with a changing profile. *J Reprod Med* 1999; 44: 698–704.
170 Cohle SD, Petty CS. Sudden death caused by embolization of trophoblast from hydatidiform mole. *J Forensic Sci* 1985; 30: 1279–1283.
171 Bakri YN, Berkowitz RS, Khan J, *et al.* Pulmonary metastases of gestational trophoblastic tumor. Risk factors for early respiratory failure. *J Reprod Med* 1994; 39: 175–178.
172 Twiggs LB. Nonneoplastic complications of molar pregnancy. *Clin Obstet Gynecol* 1984; 27: 199–210.
173 Watanabe S, Shimokawa S, Sakasegawa K, *et al.* Choriocarcinoma in the pulmonary artery treated with emergency pulmonary embolectomy. *Chest* 2002; 121: 654–656.
174 Jaffe RB, Koschmann EB. Septic pulmonary emboli. *Radiology* 1970; 96: 527–532.
175 Shiota Y, Arikita H, Horita N, *et al.* Septic pulmonary embolism associated with periodontal disease: reports of two cases and review of the literature. *Chest* 2002; 121: 652–654.
176 Cook RJ, Ashton RW, Aughenbaugh GL, *et al.* Septic pulmonary embolism: presenting features and clinical course of 14 patients. *Chest* 2005; 128: 162–166.
177 Wong KS, Lin TY, Huang YC, *et al.* Clinical and radiographic spectrum of septic pulmonary embolism. *Arch Dis Child* 2002; 87: 312–315.
178 Sakuma M, Sugimura K, Nakamura M, *et al.* Unusual pulmonary embolism: septic pulmonary embolism and amniotic fluid embolism. *Circ J* 2007; 71: 772–775.
179 Vassiloyanakopoulos A, Falagas ME, Allamani M, *et al.* *Aspergillus fumigatus* tricuspid native valve endocarditis in a non-intravenous drug user. *J Med Microbiol* 2006; 55: 635–638.
180 Celikel TH, Muthuswamy PP. Septic pulmonary emboli secondary to internal jugular vein phlebitis (postanginal sepsis) caused by *Eikenella corrodens*. *Am Rev Respir Dis* 1984; 130: 510–513.
181 Riordan T, Wilson M. Lemierre's syndrome: more than a historical curiosa. *Postgrad Med J* 2004; 80: 328–334.
182 Bentley TP, Brennan DF. Lemierre's Syndrome: Methicillin-resistant *Staphylococcus aureus* (MRSA) finds a new home. *J Emerg Med* 2008 (in press).

183 Hagelskjaer Kristensen L, Prag J. Human necrobacillosis, with emphasis on Lemierre's syndrome. *Clin Infect Dis* 2000; 31: 524–532.
184 Kuhlman JE, Fishman EK, Teigen C. Pulmonary septic emboli: diagnosis with CT. *Radiology* 1990; 174: 211–213.
185 Kwon WJ, Jeong YJ, Kim KI, *et al.* Computed tomographic features of pulmonary septic emboli: comparison of causative microorganisms. *J Comput Assist Tomogr* 2007; 31: 390–394.
186 Huang RM, Naidich DP, Lubat E, *et al.* Septic pulmonary emboli: CT-radiographic correlation. *AJR Am J Roentgenol* 1989; 153: 41–45.
187 Dalen JE, Haffajee CI, Alpert JS 3rd, *et al.* Pulmonary embolism, pulmonary hemorrhage and pulmonary infarction. *N Engl J Med* 1977; 296: 1431–1435.
188 Balakrishnan J, Meziane MA, Siegelman SS, *et al.* Pulmonary infarction: CT appearance with pathologic correlation. *J Comput Assist Tomogr* 1989; 13: 941–945.
189 MacMillan JC, Milstein SH, Samson PC. Clinical spectrum of septic pulmonary embolism and infarction. *J Thorac Cardiovasc Surg* 1978; 75: 670–679.
190 Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med* 2001; 345: 1318–1330.
191 Dodd JD, Souza CA, Muller NL. High-resolution MDCT of pulmonary septic embolism: evaluation of the feeding vessel sign. *AJR Am J Roentgenol* 2006; 187: 623–629.
192 Kuhlman JE, Fishman EK, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. *Radiology* 1985; 157: 611–614.
193 Kim Y, Lee KS, Jung KJ, *et al.* Halo sign on high resolution CT: findings in spectrum of pulmonary diseases with pathologic correlation. *J Comput Assist Tomogr* 1999; 23: 622–626.
194 Greenfield LJ, Proctor MC. Vena caval filter use in patients with sepsis: results in 175 patients. *Arch Surg* 2003; 138: 1245–1248.
195 Young T, Tang H, Aukes J, *et al.* Vena caval filters for the prevention of pulmonary embolism. *Cochrane Database Syst Rev*, 2007: CD006212.
196 Panidis IP, Kotler MN, Mintz GS, *et al.* Clinical and echocardiographic correlations in right heart endocarditis. *Int J Cardiol* 1984; 6: 17–34.
197 Golpe R, Marin B, Alonso M. Lemierre's syndrome (necrobacillosis). *Postgrad Med J* 1999; 75: 141–144.
198 Gormus N, Yeniterzi M, Telli HH, *et al.* The clinical and surgical features of right-sided intracardiac masses due to echinococcosis. *Heart Vessels* 2004; 19: 121–124.
199 Gossios KJ, Kontoyiannis DS, Dascalogiannaki M, *et al.* Uncommon locations of hydatid disease: CT appearances. *Eur Radiol* 1997; 7: 1303–1308.
200 Odev K, Acikgozoglu S, Gormus N, *et al.* Pulmonary embolism due to cardiac hydatid disease: imaging findings of unusual complication of hydatid cyst. *Eur Radiol* 2002; 12: 627–633.
201 Yague D, Lozano MP, Lample C, *et al.* Bilateral hydatid cyst of pulmonary arteries: MR and CT findings. *Eur Radiol* 1998; 8: 1170–1172.
202 Lioulias A, Kotoulas C, Kokotsakis J, *et al.* Acute pulmonary embolism due to multiple hydatid cysts. *Eur J Cardiothorac Surg* 2001; 20: 197–199.
203 Karantanas AH, Bitsios G, Karaiskou E. Echinococcus of the pulmonary artery: CT, MRI and MRA findings. *Comput Med Imaging Graph* 2000; 24: 265–267.
204 Kardaras F, Kardara D, Tselikos D, *et al.* Fifteen year surveillance of echinococcal heart disease from a referral hospital in Greece. *Eur Heart J* 1996; 17: 1265–1270.
205 Bayezid O, Ocal A, Isik O, *et al.* A case of cardiac hydatid cyst localized on the interventricular septum and causing pulmonary emboli. *J Cardiovasc Surg (Torino)* 1991; 32: 324–326.
206 Ozturk E, Ozturk A, Zeyrek F, *et al.* Recurrent pulmonary microemboli secondary to primary cardiac hydatidosis. *Heart, Lung & circulation* 2007; 16: 457–459.
207 Babba H, Messedi A, Masmoudi S, *et al.* Diagnosis of human hydatidosis: comparison between imagery and six serologic techniques. *American J Trop Med Hyg* 1994; 50: 64–68.
208 Franquet T, Plaza V, Llauger J, *et al.* Hydatid pulmonary embolism from a ruptured mediastinal cyst: high-resolution computed tomography, angiographic, and pathologic findings. *J Thorac Imaging* 1999; 14: 138–141.
209 Ilic S, Parezanovic V, Djukic M, *et al.* Ruptured hydatid cyst of the interventricular septum with acute embolic pulmonary artery complications. *Pediatr Cardiol* 2008; 29: 855–857.
210 Khanna D, Drehmer TJ. Intravenous drug abuse mimicking vasculitis. *South Med J* 2001; 94: 505–507.
211 Butch AJ, Yokel RA, Sigell LT, *et al.* Abuse and pulmonary complications of injecting pentazocine and tripelennamine tablets. *Clin Toxicol* 1979; 14: 301–306.
212 Fields TA. Pulmonary embolization of microcrystalline cellulose in a lung transplant recipient. *J Heart Lung Transplant* 2005; 24: 624–627.
213 Hammar SP, Williams MG, Dodson RF. Pulmonary granulomatous vasculitis induced by insoluble particulates: a case report. *Ultrastruct Pathol* 2003; 27: 439–449.
214 Adams DF, Olin TB, Kosek J. Cotton fiber embolization during angiography. A clinical and experimental study. *Radiology* 1965; 84: 678–682.
215 Kringsholm B, Christoffersen P. The nature and the occurrence of birefringent material in different organs in fatal drug addiction. *Forensic Sci Int* 1987; 34: 53–62.
216 Ganesan S, Felo J, Saldana M, *et al.* Embolized crospovidone (poly[N-vinyl-2-pyrrolidone]) in the lungs of intravenous drug users. *Mod Pathol* 2003; 16: 286–292.
217 Propp DA, Cline D, Hennenfent BR. Catheter embolism. *J Emerg Med* 1988; 6: 17–21.
218 Galdun JP, Paris PM, Weiss LD, *et al.* Central embolization of needle fragments: a complication of intravenous drug abuse. *Am J Emerg Med* 1987; 5: 379–382.
219 Robinson MJ, Nestor M, Rywlin AM. Pulmonary granulomas secondary to embolic prosthetic valve material. *Hum Pathol* 1981; 12: 759–762.
220 Peterson N, Harvey-Smith W, Rohrmann CA Jr. Radiographic aspects of metallic mercury embolism. *AJR Am J Roentgenol* 1980; 135: 1079–1081.
221 Schmid A, Tzur A, Leshko L, *et al.* Silicone embolism syndrome: a case report, review of the literature, and comparison with fat embolism syndrome. *Chest* 2005; 127: 2276–2281.
222 Kjellin IB, Boechat MI, Vinuela F, *et al.* Pulmonary emboli following therapeutic embolization of cerebral arteriovenous malformations in children. *Pediatr Radiol* 2000; 30: 279–283.
223 Pelz DM, Lownie SP, Fox AJ, *et al.* Symptomatic pulmonary complications from liquid acrylate embolization of brain arteriovenous malformations. *AJNR Am J Neuroradiol* 1995; 16: 19–26.
224 Padovani B, Kasriel O, Brunner P, *et al.* Pulmonary embolism caused by acrylic cement: a rare complication of percutaneous vertebroplasty. *AJNR Am J Neuroradiol* 1999; 20: 375–377.
225 Nguyen BD. Cardiac and hepatic seed implant embolization after prostate brachytherapy. *Urology* 2006: 68: 673.e17–673.e19.
226 Eshleman JS, Davis BJ, Pisansky TM, *et al.* Radioactive seed migration to the chest after transperineal interstitial prostate brachytherapy: extraprostatic seed placement correlates with migration. *Int J Radiat Oncol Biol Phys* 2004; 59: 419–425.
227 Stone NN, Stock RG. Reduction of pulmonary migration of permanent interstitial sources in patients undergoing prostate brachytherapy. *Urology* 2005; 66: 119–123.
228 Bendeck SE, Leung AN, Berry GJ, *et al.* Cellulose granulomatosis presenting as centrilobular nodules: CT and histologic findings. *AJR Am J Roentgenol* 2001; 177: 1151–1153.

229 Johnston B, Smith P, Health D. Experimental cotton-fibre pulmonary embolism in the rat. *Thorax* 1981; 36: 910–916.

230 Saadjian A, Gueunoun M, Philip-Joët F, *et al.* [Pulmonary hypertension secondary to talc microemboli in a HIV seropositive heroin-addict woman]. *Arch Mal Coeur Vaiss* 1991; 84: 1369–1373.

231 Parambil JG, Savci CD, Tazelaar HD, *et al.* Causes and presenting features of pulmonary infarctions in 43 cases identified by surgical lung biopsy. *Chest* 2005; 127: 1178–1183.

232 Nan DN, Fernandez-Ayala M, Iglesias L, *et al.* Talc granulomatosis. A differential diagnosis of interstitial lung disease in HIV patients. *Chest* 2000; 118: 258–260.

233 Richardson JD, Grover FL, Trinkle JK. Intravenous catheter emboli. Experience with twenty cases and collective review. *Am J Surg* 1974; 128: 722–727.

234 Fisher RG, Ferreyro R. Evaluation of current techniques for nonsurgical removal of intravascular iatrogenic foreign bodies. *AJR Am J Roentgenol* 1978; 130: 541–548.

235 Nag S, Vivekanandam S, Martinez-Monge R. Pulmonary embolization of permanently implanted radioactive palladium-103 seeds for carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1997; 39: 667–670.

236 Diaz-Ruiz MJ, Gallardo X, Castaner E, *et al.* Cellulose granulomatosis of the lungs. *Eur Radiol* 1999; 9: 1203–1204.

237 Stern WZ, Subbarao K. Pulmonary complications of drug addiction. *Semin Roentgenol* 1983; 18: 183–197.

238 Farber HW, Fairman RP, Glauser FL. Talc granulomatosis: laboratory findings similar to sarcoidosis. *Am Rev Respir Dis* 1982; 125: 258–261.

239 Chen QS, Blair HF. Accurate and efficient detection of pulmonary seed embolization in prostate iodine-125 permanent brachytherapy with a collimated gamma scintillation survey meter. *Med Phys* 2003; 30: 785–790.

240 Shaffer BA, Schmidt-Nowara WW. Multiple small opacities of metallic density in the lung. *Chest* 1989; 96: 1179–1181.

241 Smith RH, Graf MS, Silverman JF. Successful management of drug-induced tale granulomatosis with corticosteroids. *Chest* 1975; 73: 552–554.

242 Cook RC, Fradet G, English JC, *et al.* Recurrence of intravenous talc granulomatosis following single lung transplantation. *Can Respir J* 1998; 5: 511–514.

243 Fries CC, Levowitz B, Adler S, *et al.* Experimental cerebral gas embolism. *Ann Surg* 1957; 145: 461–470.

244 van Hulst RA, Klein J, Lachmann B. Gas embolism: pathophysiology and treatment. *Clin Physiol Funct Imaging* 2003; 23: 237–246.

245 Muth CM, Shank ES. Gas embolism. *New Engl J Med* 2000; 342: 476–482.

246 Porter JM, Pidgeon C, Cunningham AJ. The sitting position in neurosurgery: a critical appraisal. *Br J Anaesth* 1999; 82: 117–128.

247 Hill BF, Jones JS. Venous air embolism following orogenital sex during pregnancy. *Am J Emerg Med* 1993; 11: 155–157.

248 Mushkat Y, Luxman D, Nachum Z, *et al.* Gas embolism complicating obstetric or gynecologic procedures. Case reports and review of the literature. *Eur J Obstet Gynecol Reprod Biol* 1995; 63: 97–103.

249 Souders JE. Pulmonary air embolism. *J Clin Monit Comput* 2000; 16: 375–383.

250 Heckmann JG, Lang CJ, Kindler K, *et al.* Neurologic manifestations of cerebral air embolism as a complication of central venous catheterization. *Crit Care Med* 2000; 28: 1621–1625.

251 Orebaugh SL. Venous air embolism: clinical and experimental considerations. *Crit Care Med* 1992; 20: 1169–1177.

252 Sowell MW, Lovelady CL, Brogdon BG, *et al.* Infant death due to air embolism from peripheral venous infusion. *J Forensic Sci* 2007; 52: 183–188.

253 Ie SR, Rozans MH, Szerlip HM. Air embolism after intravenous injection of contrast material. *South Med J* 1999; 92: 930–933.

254 Dudar BM, Kim HE. Massive air embolus treated with rheolytic thrombectomy. *J Invasive Cardiol* 2007; 19: E182–E184.

255 Gregoric ID, Myers TJ, Kar B, *et al.* Management of air embolism during HeartMate XVE exchange. *Tex Heart Inst J* 2007; 34: 19–22.

256 Marini JJ, Culver BH. Systemic gas embolism complicating mechanical ventilation in the adult respiratory distress syndrome. *Ann Intern Med* 1989; 110: 699–703.

257 McGrath BJ, Zimmerman JE, Williams JF, *et al.* Carbon dioxide embolism treated with hyperbaric oxygen. *Can J Anaesth* 1989; 36: 586–589.

258 Min SK, Kim JH, Lee SY. Carbon dioxide and argon gas embolism during laparoscopic hepatic resection. *Acta Anaesthesiol Scand* 2007; 51: 949–953.

259 Menendez-Gonzalez M, Oliva-Nacarino P, Alvarez-Cofino A. Cerebral gas embolism caused by pleural fibrinolytic treatment. *Stroke* 2007; 38: 2602–2604.

260 Sharma P, Pilling JE, Awad WI. Cerebral air embolism after noninvasive ventilation postpulmonary wedge resection. *J Thorac Cardiovasc Surg* 2007; 134: 262–263.

261 Barak M, Katz Y. Microbubbles: pathophysiology and clinical implications. *Chest* 2005; 128: 2918–2932.

262 Ziser A, Adir Y, Lavon H, *et al.* Hyperbaric oxygen therapy for massive arterial air embolism during cardiac operations. *J Thorac Cardiovasc Surg* 1999; 117: 818–821.

263 Butler BD, Hills BA. The lung as a filter for microbubbles. *J Appl Physiol* 1979; 47: 537–543.

264 Durant TM, Oppenheimer MJ, Webster MR, *et al.* Arterial air embolism. *Am Heart J* 1949; 38: 481–500.

265 Palmon SC, Moore LE, Lundberg J, *et al.* Venous air embolism: a review. *J Clin Anesth* 1997; 9: 251–257.

266 Sviri S, Woods WP, van Heerden PV. Air embolism–a case series and review. *Crit Care Resusc* 2004; 6: 271–276.

267 Bove AA, Hallenbeck JM, Elliott DH. Circulatory responses to venous air embolism and decompression sickness in dogs. *Undersea Biomed Res* 1974; 1: 207–220.

268 Evans DE, Kobrine AI, Weathersby PK, *et al.* Cardiovascular effects of cerebral air embolism. *Stroke* 1981; 12: 338–344A.

269 van Blankenstein JH, Slager CJ, Soei LK, *et al.* Effect of arterial blood pressure and ventilation gases on cardiac depression induced by coronary air embolism. *J Appl Physiol* 1994; 77: 1896–1902.

270 Butler BD, Hills BA. Transpulmonary passage of venous air emboli. *J Appl Physiol* 1985; 59: 543–547.

271 Bull JL. Cardiovascular bubble dynamics. *Crit Rev Biomed Eng* 2005; 33: 299–346.

272 Flick MR, Perel A, Staub NC. Leukocytes are required for increased lung microvascular permeability after microembolization in sheep. *Circ Res* 1981; 48: 344–351.

273 Lachmann B, Eijking EP, So KL, *et al. In vivo* evaluation of the inhibitory capacity of human plasma on exogenous surfactant function. *Intensive Care Med* 1994; 20: 6–11.

274 Stewart RH, Quick CM, Zawieja DC, *et al.* Pulmonary air embolization inhibits lung lymph flow by increasing lymphatic outflow pressure. *Lymphat Res Biol* 2006; 4: 18–22.

275 Malhotra MS, Wright HC. The effects of a raised intrapulmonary pressure on the lungs of fresh unchilled cadavers. *J Pathol Bacteriol* 1961; 82: 198–202.

276 Schlimp CJ, Loimer T, Rieger M, *et al.* The potential of venous air embolism ascending retrograde to the brain. *J Forensic Sci* 2005; 50: 906–909.

277 Gorman DF, Mitchell SJ. A history of cerebral arterial gas embolism research: key publications. *S Pacific Undersea Med Soc J* 1999; 29: 34–39.

278 Van Blankenstein JH, Slager CJ, Schuurbiers JC, *et al.* Heart function after injection of small air bubbles in coronary artery of pigs. *J Appl Physiol* 1993; 75: 1201–1207.

279 Hossmann KA, Fritz H. Coupling of function, metabolism, and blood flow after air embolism of the cat brain. *Adv Neurol* 1978; 20: 255–262.
280 Johansson BB. Cerebral air embolism and the blood-brain barrier in the rat. *Acta Neurol Scand* 1980; 62: 201–209.
281 Gorman DF, Browning DM. Cerebral vasoreactivity and arterial gas embolism. *Undersea Biomed Res* 1986; 13: 317–335.
282 Meldrum BS, Papy JJ, Vigouroux RA. Intracarotid air embolism in the baboon: effects on cerebral blood flow and the electroencephalogram. *Brain Res* 1971; 25: 301–315.
283 Mitchell S, Gorman D. The pathophysiology of cerebral arterial gas embolism. *J Extra Corpor Technol* 2002; 34: 18–23.
284 Pekna M, Nilsson L, Nilsson-Ekdahl K, *et al.* Evidence for iC3 generation during cardiopulmonary bypass as the result of blood-gas interaction. *Clin Exp Immunol* 1993; 91: 404–409.
285 Lynch JJ, Schuchard GH, Gross CM, *et al.* Prevalence of right-to-left atrial shunting in a healthy population: detection by Valsalva maneuver contrast echocardiography. *Am J Cardiol* 1984; 53: 1478–1480.
286 Tommasino C, Rizzardi R, Beretta L, *et al.* Cerebral ischemia after venous air embolism in the absence of intracardiac defects. *J Neurosurg Anesthesiol* 1996; 8: 30–34.
287 Katz J, Leiman BC, Butler BD. Effects of inhalation anaesthetics on filtration of venous gas emboli by the pulmonary vasculature. *Br J Anaesth* 1988; 61: 200–205.
288 Dutka AJ. A review of the pathophysiology and potential application of experimental therapies for cerebral ischemia to the treatment of cerebral arterial gas embolism. *Undersea Biomed Res* 1985; 12: 403–421.
289 Tovar EA, Del Campo C, Borsari A, *et al.* Postoperative management of cerebral air embolism: gas physiology for surgeons. *Ann Thorac Surg* 1995; 60: 1138–1142.
290 Blanc P, Boussuges A, Henriette K, *et al.* Iatrogenic cerebral air embolism: importance of an early hyperbaric oxygenation. *Intensive Care Med* 2002; 28: 559–563.
291 Bedford RF, Marshall WK, Butler A, *et al.* Cardiac catheters for diagnosis and treatment of venous air embolism: a prospective study in man. *J Neurosurg* 1981; 55: 610–614.
292 Russell GB, Graybeal JM. Detection of venous air embolism: comparison of oxygenation and ventilation monitoring methods in dogs. *J Neurosurg Anesthesiol* 1992; 4: 36–40.
293 Gildenberg PL, O'Brien RP, Britt WJ, *et al.* The efficacy of Doppler monitoring for the detection of venous air embolism. *J Neurosurg* 1981; 54: 75–78.
294 Schafer ST, Lindemann J, Brendt P, *et al.* Intracardiac transvenous echocardiography is superior to both precordial Doppler and transesophageal echocardiography techniques for detecting venous air embolism and catheter-guided air aspiration. *Anesth Analg* 2008; 106: 45–54.
295 Smith RM, Van Hoesen KB, Neuman TS. Arterial gas embolism and hemoconcentration. *J Emerg Med* 1994; 12: 147–153.
296 Voorhies RM, Fraser RA. Cerebral air embolism occurring at angiography and diagnosed by computerized tomography. Case report. *J Neurosurg* 1984; 60: 177–178.
297 Hodgson M, Beran RG, Shirtley G. The role of computed tomography in the assessment of neurologic sequelae of decompression sickness. *Arch Neurol* 1988; 45: 1033–1035.
298 Weiss KL, Macura KJ, Ahmed A. Cerebral air embolism: Acute imaging. *J Stroke Cerebrovasc Dis* 1998; 7: 222–226.
299 Toung T, Ngeow YK, Long DL, *et al.* Comparison of the effects of positive end-expiratory pressure and jugular venous compression on canine cerebral venous pressure. *Anesthesiology* 1984; 61: 169–172.
300 Van Liew HD, Conkin J, Burkard ME. The oxygen window and decompression bubbles: estimates and significance. *Aviat Space Environ Med* 1993; 64: 859–865.
301 De Angelis J. A simple and rapid method for evacuation of embolized air. *Anesthesiology* 1975; 43: 110–111.
302 Moon RE, de Lisle Dear G, Stolp BW. Treatment of decompression illness and latrogenic gas embolism. *Respir Care Clin N Am* 1999; 5: 93–135.
303 Hoffman WE, Charbel FT, Edelman G, *et al.* Thiopental and desflurane treatment for brain protection. *Neurosurgery* 1998; 43: 1050–1053.
304 Leitch DR, Hallenbeck JM. Oxygen in the treatment of spinal cord decompression sickness. *Undersea Biomed Res* 1985; 12: 269–289.
305 Thom SR, Mendiguren I, Hardy K, *et al.* Inhibition of human neutrophil β2-integrin-dependent adherence by hyperbaric O_2. *Am J Physiol* 1997; 272: C770–C777.
306 Dexter F, Hindman BJ. Recommendations for hyperbaric oxygen therapy of cerebral air embolism based on a mathematical model of bubble absorption. *Anesth Analg* 1997; 84: 1203–1207.
307 Wherrett CG, Mehran RJ, Beaulieu MA. Cerebral arterial gas embolism following diagnostic bronchoscopy: delayed treatment with hyperbaric oxygen. *Can J Anaesth* 2002; 49: 96–99.
308 Boussuges A, Blanc P, Molenat F, *et al.* Haemoconcentration in neurological decompression illness. *Int J Sports Med* 1996; 17: 351–355.
309 Reasoner DK, Ryu KH, Hindman BJ, *et al.* Marked hemodilution increases neurologic injury after focal cerebral ischemia in rabbits. *Anesth Analg* 1996; 82: 61–67.
310 Nishimoto K, Wolman M, Spatz M, *et al.* Pathophysiologic correlations in the blood-brain barrier damage due to air embolism. *Adv Neurol* 1978; 20: 237–244.
311 Francis TJ, Dutka AJ. Methyl prednisolone in the treatment of acute spinal cord decompression sickness. *Undersea Biomed Res* 1989; 16: 165–174.
312 Mitchell SJ, Pellett O, Gorman DF. Cerebral protection by lidocaine during cardiac operations. *Ann Thorac Surg* 1999; 67: 1117–1124.
313 Spahn DR. Current status of artificial oxygen carriers. *Adv Drug Deliv Rev* 2000; 40: 143–151.
314 Moon RE. Adjuvant therapy in decompression illness: present and future. *S Pacific Undersea Med Soc J* 2000; 30: 99–110.
315 Dujic Z, Palada I, Valic Z, *et al.* Exogenous nitric oxide and bubble formation in divers. *Med Sci Sports Exerc* 2006; 38: 1432–1435.