Fatal pulmonary embolism: a retrospective clinical study conducted in women aged between 18 to 45 years and review of the literature

Embolismul pulmonar fatal: studiu clinic retrospectiv pe femei cu vârsta între 18 şi 45 ani şi o recenzie a literaturii

Eugen B. Petcu[1*], Timothy D. Koelmeyer[2], Rodica I. Miroiu[3], Leonard Berman[4], Valentin Ghiorghiu[5], Maria M. Opris[6]

1 Griffith University School of Medicine, Australia
2 The University of Auckland and Auckland Public Hospital, New Zealand
3 National Sport University, Bucharest, Romania
4 Boston University Medical Center, Mallory Institute of Pathology, Boston, USA
5 Legal Medicine National Institute "Mina Minovici", Bucharest, Romania
6 University of Medicine and Pharmacy Tg. Mureş, Romania

Abstract

Aim*: Pulmonary embolism (PE) and deep venous thrombosis (DVT) represent components of the same pathological entity, the venous thromboembolism (VTE). Recent epidemiological studies suggest that in certain conditions women of reproductive age may be prone to develop fatal PE. This retrospective study evaluates the risk factors of fatal PE in women of reproductive age between 18 to 45 years, in the light of data from scientific literature.*Methods and Results*: The files from sixteen consecutive fatal cases of PE recorded in women over 10 years (1990-1999) were retrieved from the archive of the Forensic Pathology Section at the Faculty of Medicine in Auckland, New Zealand. The demographic data and the pathologist's histological report including the final diagnosis were closely correlated. Obesity was the only pathological finding in four cases (25%) although it was also found associated with other risk factors in another five cases (31%). Cardiovascular disease and deep venous thrombosis were identified as major risk factors of PE in three cases each (18%). Malignancy, oral contraceptive administration and postpartum thromboembolism were reported in three separate cases. In two patients, it was not possible to identify the cause of fatal pulmonary thromboembolism.* Discussion and Conclusions*: Our observations appear to indicate that obesity is the most important risk factor for fatal pulmonary thromboembolism in women of child-bearing age. Numerous studies have shown that obesity may play this role by bringing about and perpetuating an inflammatory state which then leads to thrombosis through a variety of mechanisms, including the prothrombotic action of some adipose tissue hormones and abnormal fibrinolysis and coagulation in the background of endothelial dysfunction. Obesity may also be associated with various other risk factors or*

*Corresponding author:** Eugen B. Petcu, MHSc, MD, PhD, FASCP, FCAP
tel: 61 41029 5981, E-mail: e.petcu@griffith.edu.au

pathological conditions in which thrombosis occurs via several other recognized pathways. Due to the prime etiological significance of obesity, it is reasonable to refer to this condition as "(fatal) obesity-related pulmonary embolism" (ORPE). It would thus follow that if pulmonary embolism appears not to be associated with obesity, these cases should be referred to as "(fatal) non-obesity related pulmonary embolism" (NORPE). In case of over-weight or obese patients, the prophylaxis against fatal PE should start early and should always include drug therapy and weight loss programs which would be designed to diminish or lessen the prothrombotic factors leading to VTE.

Keywords: obesity related pulmonary embolism, fatal pulmonary embolism, coagulation, fibrinolysis, endocrine organ.

Rezumat

Scopul studiului*: Trombembolismul pulmonar şi tromboza venoasă profundă reprezintă componente ale aceleiaşi entităţi patologice – trombembolismul venos. Studii epidemiologice recente au sugerat că, în anumite condiţii, femeile în perioada fertilă pot fi predispuse trombembolismului pulmonar fatal. Acest studiu retrospectiv îşi propune să evalueze factorii de risc pentru trombembolism fatal la femei cu vârste cuprinse între 18 şi 45 ani, prin prisma datelor din literatura de specialitate.* Material, metodă, rezultate: *Datele de la 16 cazuri fatale, consecutive, la femei, într-un interval de peste 10 ani (1990 – 1999), au fost colectate din arhiva secţiei de anatomopatologie a Facultăţii de Medicină din Auckland, New Zealand. S-au corelat datele demografice cu raportul anatomo-patologic şi diagnosticul final. În 25% din cazuri obezitatea a fost singurul factor patologic identificat, aceasta asociindu-se cu alţi factori de risc la alte cinci cazuri (31%). În trei cazuri s-a decelat afectare cardiovasculară şi tromboză venoasă profundă (18%). În alte trei cazuri au fost implicate malignitatea, consumul de contraceptive orale şi trombembolismul postpartum. La două dintre paciente nu a fost găsită cauza trombembolismului fatal.* Discuţii şi concluzii*: Observaţiile noastre au indicat faptul că obezitatea la femeile în perioda fertilă pare să fie factorul de risc cel mai important pentru embolismul pulmonar fatal. Numeroase studii au demonstrat că obezitatea stă la baza instalării şi perpetuării unui status inflamator care predispune la tromboză prin diferite mecanisme, care includ activitatea protrombotică a unor hormoni din ţesutul adipos, alături de perturbarea fibrinolizei şi a procesului de coagulare prin disfuncţie endotelială. Obezitatea este deseori asociată cu alţi factori de risc şi condiţii patologice care induc tromboză. Facem referire la trombembolism pulmonar fatal legat de obezitate în cazurile în care obezitatea reprezintă factorul etiologic primordial şi trombembolism pulmonar fatal fără legătură cu obezitatea în cazurile în care obezitatea nu este implicată. În consecinţă profilaxia trombembolismului pulmonar trebuie începută devreme în cazul tuturor pacientelor supraponderale şi obeze, atât prin terapie medicamentoasă cât şi prin programe care vizează pierderea în greutate, în scopul diminuării şi eliminării factorilor favorizanţi ai trombembolismului venos.*

Cuvinte cheie: trombembolism pulmonar fatal, obezitate, coagulare, fibrinoliză, glande endocrine

Introduction

Epidemiological studies conducted in the United States have suggested that for a population of 100,000, there are 100 thromboembolic events for the first time. In this population, the incidence of venous thromboembolism (VTE) increases from less than five cases in those younger than 15 years of age to 500 cases in those aged above 80 (0.5%) (1). In normal conditions, coagulation is initiated by Tissue Factor (TF) which binds factor VII. Subsequently the coagulation cascade is turned-on with activation of factors X, IX, VIII, V and thrombin. The last one converts fibrinogen into a fibrin network in which platelets become trapped and eventually form the blood clot. This is removed by plasmin. However, fibrinolysis is counteracted by plasminogen-activator inhibitor-1 (PAI-1) (2). In theory, any

factor that enhances coagulation or increases the action of PAI-1 would promote VTE. After thrombus formation in the lumen of a deep vein, part of the clot may become loose and forms emboli which travel to the lungs via the pulmonary arteries. Interestingly, some authors have suggested that there is a higher risk of developing the deep venous thrombosis/pulmonary embolism (DVT/PE) sequence if the initiating prothrombotic insult is more severe (3).

The PE is a potentially fatal occurrence characterized by hypotension, dyspnea, tachycardia with or without right heart dysfunction, which must be treated as a true medical emergency (4). Thus, diagnostic investigation and appropriate antithrombotic therapy consisting of low-molecular-weight heparin and warfarin, or any other suitable anticoagulant, must be initiated as soon as possible (5). Unfortunately, in 25% of cases the PE is lethal (6). Hull et al (7) have reported 150,000 to 200,000 deaths per year from PE in the United States alone.

Although Wirchow speculated as early as the XIX century that stasis, endothelial injury and abnormalities in blood coagulation could be the factors promoting the initial thrombosis leading to venous thromboembolism (8), it has recently been shown that some of the risk factors related to cardiovascular disease such as obesity, hypertension, diabetes, smoking and hypercholesterolemia are also associated with DVT/PE (9). Moreover, the gender and the hormonal profile of the patients could also be crucial in determining the risk for thromboembolism. Hoffmann et al (10) have shown in a very recent study that in Europe and North America, age-standardized PE mortality is generally higher in women than in men (with the exception of Poland). Pomp ER et al (11) have shown that pregnant women have a two to five fold higher frequency of DVT and PE compared with non-pregnant women of comparable child bearing age. Also, the number of fatal cases of VTE associated with pregnancy is similar to the number of VTE-related deaths recorded after

intake of oral contraceptives. As expected in those circumstances the impact of these findings is most important in the youngest sexually active age group (12).

Overall, it appears that women of child bearing age might be at increased risk for developing fatal PE compared with the rest of the population. The aim of this study was to quantify and evaluate these risk factors in women aged 18 to 45 as recorded in the Forensic Pathology Section at the Faculty of Medicine and Auckland Public Hospital, New Zealand, during the years 1990-1999, when the deceased were routinely subject to a coroner directed autopsy.

Over the past few years, recent research has revealed new insights into the molecular mechanisms of the of the DVT/PE pathogenesis sequence. We have attempted to evaluate our cases based on these new findings. We will also undertake an updated review of DVT/PE thrombogenesis, which will be presented along with the results of this study.

Methods and results

Records of autopsies performed on women 18 to 45 years-old were selected from the archives of the Forensic Pathology Section of the Faculty of Medicine and Auckland Public Hospital. Only forensic cases were reviewed; no medical autopsies were included.

In the period 1990 to 1999, 15,087 Coroner directed necropsies were performed for the Auckland area, where just over a million people live. There were a total of sixteen cases of fatal PE found in this material. All autopsies were performed less than 12 hours post-mortem. Our standard protocol included the case history, medications, demographic information including age and race, and weight and height measurements. We have also determined the excess body fat in terms of the body mass index (BMI), the ratio of the square of patient's weight divided by her height. The microscopic information for each subject was also carefully

Table1. Demographic data

AGE (years)	
mean	36.37
median	37.5
RACE	
Maori	4
Caucasian	10
Polynesian	1
Indian	1
RISK FACTORS	
Idiopathic	2
Obesity only	4
CV disease	3
Venous thrombosis	3
Malignancy	2
Postpartum	1
Oral contraceptives	1

reviewed. The anatomical diagnosis of pulmonary embolism as a probable cause of death as well as the presence of other related anatomic-pathological conditions was verified in each of the subjects selected in our series.

As seen in *Table 1*, most of the patients were Caucasians and several risk factors were identified.

Our findings consisted of two cases of primary fatal idiopathic PE and 14 cases of fatal PE found in conjunction with other conditions. Only three patients (18%) showed unequivocal evidence of deep venous thrombosis (DVT). One of these, a 42 year old Caucasian woman, developed DVT in the setting of obesity. Cancer was found in association with obesity on one occasion while a second case of cancer was encountered in a non-obese patient. Extensive atherosclerosis was seen in one obese patient and a second developed severe heart failure prior to death. Also, fatal PE occurred in another obese woman who was using oral contraceptives, and in two non-obese subjects, one with congenital heart disease, and one who died postpartum. Interestingly, in four cases only obesity was noted as a risk factor for PE. Overall, obesity was noted in nine of our cases of fatal PE (56%). As noted above, in five of

these, it was associated with a number of other possible risk factors, such as DVT (1 case), cancer (1 case), cardiovascular disease (2 cases) and oral contraceptives intake (1 case) (*Table2).*

Discussion

In New Zealand, Coroner directed postmortem examinations are performed in cases of trauma or if the death is natural but the cause is unknown. Our study involved only Coroner directed autopsies on cases of non-traumatic death in women between 18 to 45 years of age. All the cases were natural deaths and some subjects had known chronic conditions but the cause of death was initially poorly understood.

Although in most of these cases we were able to identify risk factors for thrombosis, no prophylactic antithrombotic treatment was administered, with the exception of a young woman aged 23 who was taking aspirin after an episode of DVT. The evaluated fatal PE cases represent 0.1% of the total number of forensic autopsies performed in the Forensic Pathology Section of the Auckland Public Hospital and Faculty of Medicine. Interestingly, this incidence is lower than in other reports. For example, Ely SF et al (13) mention that fatal PE represents 0.8% of the total number of autopsies performed in New York City. Others have published even higher values. Hamanaka et al (14) have found that the incidence of fatal PE among psychiatric patients treated with neuroleptics at a large Japanese medical center could reach 2.5% of the total forensic cases. Other authors from Ontario, Canada have reported that fatal PE may be found in 5 to 10% of deaths recorded in medical patients (15). These higher numbers of fatal PE encountered in hospitalized patients may be explained by the associated complex pathology in which several pro-thrombotic risk factors may be involved. In addition, the above mentioned studies have evaluated all the patients regardless the gender or the age of patients whereas our series has evaluated only a specific population of a well defined age.

Idiopathic fatal PE

For didactic reasons, we have divided our cases into primary or idiopathic, and secondary PE. Only two cases were categorized as the former. The first was a 35 year-old Caucasian female who presented with hypotension and hyperventilation, and died shortly after hospital admission. Necropsy revealed bilateral PE, in which the lumen of the main pulmonary artery was over 70% obstructed. No other findings were noted. The second case was a 23 year-old Caucasian female who died shortly after being admitted for pneumonia. Thrombosis was identified in both pulmonary arteries and the vena cava. This patient had had a history of DVT in the immediate past but no morphological evidence of this was noted post-mortem. In addition the patient was taking aspirin and was not known to have any other pro-thrombotic risk factors.

Fatal obesity related and non-obesity related fatal PE (fatal ORPE and NORPE)

As mentioned before, nine (56%) of our subjects were obese. In the Framingham study, women who died after developing PE had higher weights on average than those who died from other causes (16). It is therefore not surprising that the majority of our cases were associated with obesity. The morphological diagnosis of PE was readily confirmed in all obese subjects. However, although our cases were strongly associated with obesity, they were also variably associated with other findings and conditions that are separately recognized as PE risk factors such as: DVT, malignancy, cardiovascular disease and oral contraceptive intake (*Table 2)*.

By World Health Organization (WHO) standards a patient is obese if the calculated BMI is over 30 kg/m^2. According to the WHO obesity is classified into three distinct categories: grade I (BMI=30 to 34.9 kg/m^2), grade II (BMI=35 to 39.9 kg/m^2) and grade III (BMI more than 40 kg/m^2) (17, 18). In our subjects, BMI varied between 30.59 and 75.09 kg/m^2 (*Table 3)*.

As shown above in four cases obesity was the only risk factor for fatal PE. Interestingly, three of these women had grade I. This suggests that even a mild increase of the BMI may induce a pro-thrombotic state with catastrophic consequences. The important question in these circumstances is how obesity leads to fatal PE and which are the pathways and factors involved in this process?

The pathogenesis of PE in the background of obesity may be explained if we accept the premise that adipose tissue is in essence an endocrine organ which secretes among other substances several pro-thrombotic factors.

Hormones secreted by adipose tissue

a. Leptin

Energy expenditure and body weight appear to be modulated by leptin, an adipocyte-derived cytokine. Leptin acts via the hypothalamus to regulate glucose and fat metabolism, also suppressing food intake (19). The level of leptin appears to be directly proportional to the amount of adipose tissue. Thus, an increase in leptin has been recorded in pregnant women as their body mass index increases (20). It has also been shown that leptin promotes coagulation in leukocyte and monocyte cultures by releasing tissue factor (TF) (21). Moreover, leptin promotes a pro-thrombotic state by acting directly on its functional receptor located on platelets via tyrosine-phosphorylation of Gq alpha-subunits located on these cells (22, 23). Clinically, leptin's pro-thrombotic role has been demonstrated in experiments which showed that platelets from obese patients have an enhanced aggregating response to ADP, which is a known platelet aggregating promoter (24).

b. Adiponectin

Adiponectin is produced solely by adipocytes and its production is inversely proportional to increased weight, BMI and C-reactive protein levels (25). In fact, its high levels in lean subjects act as anti-inflammatory stimulus while lowering its level as a result of increased body mass index (BMI) results in an enhanced production by monocytes of an "inflammatory soup" composed of IL-1 beta, TNF-alpha and IL-6 (26).

Table 2. Detailed demographic and medical data of the patients

No	Age	Race	Medication	History	Obesity	Observations/Cause of death
1	45	Caucasian	nil	Pregnancy	no	Thrombi in both pulmonary arteries Postpartum PE
2	42	Polynesian	nil	nil	yes/163 kg/157 cm	Thrombi in both pulmonary arteries ***PE sec to obesity***
3	38	Caucasian	nil	nil	yes/98 kg/ 165 cm	Atherosclerosis of the LAD coronary Circumflex mildly occluded Thrombi in left pulmonary artery ***PE sec to obesity and CV disease***
4	31	Indian	nil	Systemic Amiloidosis Hepatitis type B, Immobility	no	DVT of the left lower limb, Thrombi in both pulmonary arteries PE secondary to DVT
5	42	Caucasian	nil	nil	yes/109 kg/169 cm	DVT of the left lower limb Thrombi in both pulmonary arteries ***PE sec to obesity and DVT***
6	45	Maori	nil	nil	yes/97 kg/171 cm	Thrombi at bifurcation of pulmonary artery ***PE sec to obesity***
7	35	Caucasian	nil	Hypotension, Hyper-ventilation prior to death	no	Thrombi in both pulmonary arteries Idiopathic PE
8	23	Caucasian	Aspirin	Past history of DVT Pneumonia	no	Thrombi at bifurcation of pulmonary artery Idiopathic PE

Table 2. Detailed demographic and medical data of the patients (*continued*)

No	Age	Race	Medication	History	Obesity	Observations/Cause of death
9	37	Maori	nil	Hyperparathyroidism Hepatic steatosis Endometrial carcinoma Obstructive sleep apnea	yes/199 kg/ 163 cm	Thrombi in both pulmonary arteries ***PE sec to obesity and cancer***
10	36	Caucasian	Oral contraceptives	Smoker 20 cigarettes per day	yes/93 kg/ 168 cm	Subcapsular liver nodules Thrombi in both pulmonary arteries ***PE sec to obesity and OC intake***
11	27	Caucasian	nil	Tricuspid atresia Atrial Fibrillation prior to death	no	Cardiac thrombi Thrombi at bifurcation of pulmonary artery PE sec to congenital CV disease
12	32	Maori	Paracetamol	Schizophrenia	yes/106 kg/ 177 cm	Thrombi in the main pulmonary artery ***PE sec to obesity***
13	44	Caucasian	nil	nil	yes/82 kg/ 164 cm	Thrombi in the main pulmonary artery ***PE sec to obesity***
14	22	Caucasian	Atropine, Adrenaline prior to death	Collapsed during warming up for rugby	no	DVT of the left lower limb Thrombi in both pulmonary arteries PE sec to DVT
15	39	Maori	nil	Congestive Heart Failure	yes/157 kg/ 166 cm	Left Ventricular Hypertrophy Left Atrial Hypertrophy Thrombi in the left pulmonary artery ***PE sec to obesity and CV disease***
16	44	Caucasian	nil	Ovarian cancer LeVeen shunt	no	Thrombi at bifurcation of pulmonary artery PE sec to cancer

Table 3. Fatal cases of PE associated with obesity

Patient (selection number)	Age (years)	Race	Body weight (kg)	Height (m)	BMI (Kg/m2)	Obesity
2*	42	Polynesian	163	1.57	66.26	grIII, morbid
3	38	Caucasian	98	1.65	36.02	grII, moderate
5	42	Caucasian	109	1.69	38.24	grII, moderate
6*	45	Maori	97	1.71	33.21	grI, mild
9	37	Maori	199	1.63	75.09	grIII, morbid
10	36	Caucasian	93	1.68	32.97	grI, mild
12*	32	Maori	106	1.77	33.86	grI, mild
13*	44	Caucasian	82	1.64	30.59	grI, mild
15	39	Maori	157	1.66	57.09	grIII, morbid

* In these cases obesity was the only risk factor for thromboembolism

It appears that the site of action of adiponectin is probably the hypothalamus, where it acts on its two receptors, R1 and R2 which are co-localized with the leptin receptors. Experimental evidence seems to suggest that these receptors modulate the energy balance by stimulation of the AMP activated protein kinase pathway (27). In addition, adiponectin is inversely proportional to the PAI-1 level (25). Overall, all evidence appears to indicate that high levels of adiponectin regulates energy consumption, thus tending to modulate and prevent thrombosis.

c. Resistin

Clinical and experimental studies have revealed that this cytokine can also be synthesised by adipose tissue and macrophages. Resistin rises in parallel with C-reactive protein, IL-6, TNF-alpha, procalcitonin and leukocytosis (28). However, neither its direct effects nor the molecular mechanism of its action are clearly understood at this time. Neither do we know if it interferes directly with coagulation and/or fibrinolysis.

Obesity as a pro-thrombotic inflammatory state

Lemieux et al (29) have shown in men with atherogenic dyslipidemia and insulin resistance syndrome that obesity and accumulation of abdominal adipose tissue correlate strongly with increasing levels of C-reactive protein (CRP). However, in atherogenesis, an increasing CRP level is associated with the risk of serious complications, including increasing plaque volume and sudden coronary death (30-32). In this context, statins and aspirin appear to decrease the thrombotic and plaque rupture risk by reducing the level of C-reactive protein (33, 34). Thus, obesity may be regarded as a form of pro-thrombotic inflammatory state.

In atherosclerosis, CRP exerts its action via a variety of factors. Recent research has shown that in response to CRP, human mononuclear cells synthesize increased amounts of cytokines such as tumour necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1) and matrix metalloproteinase-9 (MMP 9) (35). All of these promote endothelial dysfunction by attracting leukocytes at a vascular injury site and up-regulating cell adhesion molecules. In addition, they promote smooth muscle cell migration into the intima, where they proliferate and acquire phagocytic properties, becoming foamy cells by absorbing oxidized lipoproteins. This leads to the formation of plaque, which may ultimately rupture and initiate thrombus formation (36-41). Notably, in obese women, weight loss can induce the normalization of the cytokines levels, and the recovery of the endothelial dysfunction (42, 43).

In regard to hemostasis, experimental studies have shown that TNF-alpha, which as mentioned above may be produced after CRP stimulation, increases the levels of plasminogen activating inhibitor-1 (PAI-1) and tissue factor (TF), which subsequently promote coagulation and thrombosis (44, 45). Moreover, acute phase reactions characterized as described above by increased levels of CRP, are associated with elevated levels of fibrinogen, which is synthesized subsequent to autocrine and paracrine activation of monocytes by IL-6 (46).

Obesity and abnormalities of coagulation

Tissue factor (TF)

Recent clinical evidence suggests that mononuclear leukocytes from obese patients express increased amounts of TF. Also, in healthy subjects, leptin promotes synthesis of TF by mononuclear cells in a dose dependent-manner through a JAK2-dependent mechanism with participation of TNF-alpha (47).

Fibrinogen

Mingers and Ströder (48) have reported increased levels of fibrinogen in overweight but otherwise healthy children. Also, obese women present with an increased level of fibrinogen which returns to normal after dieting (49). Remarkably, fibrinogen stimulates endothelial cell proliferation by its binding to fibroblast growth factor 2 (FGF-2), fibrin and vascular endothelial growth factor (50, 51). Also, it forms a scaffold, promoting vascular smooth muscle development leading to atheroma and thrombosis via fibrin formation (52, 53). In addition, in vitro fibrinogen acts via modulation of Ca ion on smooth muscle and endothelial cells to promote vascular changes similar with those seen in thromboembolic pulmonary hypertension (54).

Factor VII

It is known that increased levels of factor VII is associated with hypercoagulability. Clinical evidence indicates that a significantly increased level of factor VII is associated with obesity and female sex (55, 56). However, the factor VII level returns to normal with just a modest weight loss (57).

Obesity and abnormalities of fibrinolysis

In general, thrombosis is promoted either by decreased tissue-type plasminogen active factor (t-PA) or an increased plasminogen activator inhibitor1 (PAI-1). Endothelial release of t-PA regulates fibrinolysis and is considered to be a primary endogenous defense mechanism against thrombosis. Van Guilder et al (58) have found that in obese and overweight patients, the net release of t-PA is 45% lower than in normal non-obese individuals. However, the level of t-PA returns to normal after regular aerobic exercise that increases the capacity of endothelium to release t-PA (58).

PAI-1 may be produced by adipocytes (59). PAI-1 gene expression is associated with obesity and may modulate the changes in adipose tissue distribution which are noted at menopause (60). Moreover, in obese patients with arterial and venous thrombosis, the decrease in total fibrinolytic activity appears to be caused by an increase in PAI-1 levels (61). Interestingly, the high levels of PAI-1 seen in obese patients are promoted by an increased production of TGF-beta, which is released by an enlarged mass of adipose tissue (62).

All of the above clinical and experimental studies (including our own) point to the central role of obesity in the etiopathogenesis of fatal PE. In consideration of the fact that obesity has reached pandemic proportions in the developed world, the therapeutic and socio-economic implications are that PE should be further classified by the presence or absence of obesity. Therefore, it reasonable to describe those cases of pulmonary embolism associated with obesity as "(fatal) obesity-related pulmonary embolism" (ORPE). If obesity is not associated with pulmonary embolism, these cases should be labeled "(fatal) non-obesity related pulmonary embolism" (NORPE). In case of overweight or obese patients, the prophylaxis against fatal PE should start early and should always include weight loss and physical exercise programs, and which would favor the balance of thrombolytic over pro-thrombotic factors.

Fatal PE post-DVT

As mentioned above, DVT and PE represent forms of the same pathophysiological process, i.e. VTE, and both are associated with the same risk factors. PE however is usually a more advanced stage of this process where the thrombus has broken off and embolized to a distant site, i.e. the lung. Usually, DVT develops at the site of a local insult in the deep venous network. At this level, the blood flow is slow and as a result fibrin and platelets accumulate and initiate thrombus formation. DVT however may be clinically silent and therefore very difficult to diagnose. Thus, the true incidence of DVT is very difficult to determine due to missed clinical detection (63).

In our study we have identified three unequivocal cases of fatal PE subsequent to well documented DVT. One such case occurred in a 42 year-old obese Caucasian woman (BMI= 38.24 Kg/m^2) in which the thrombotic process involved the deep veins of the left leg and the development of pulmonary emboli in the smaller arterial branches. No other risk factors were evident. However, one can speculate that the association of obesity, an inflammatory state characterized by abnormalities of coagulation, platelet aggregation and fibrinolysis, significantly increased the risk of fatal PE after the initial DVT.

Another case of fatal PE after an episode of DVT was encountered in a 31 year-old Indian woman with amyloidosis and hepatitis B. Post-mortem examination revealed thrombi in the deep veins of the left lower limb and in the main branches of the pulmonary artery. Prolonged immobility due to her underlying conditions was noted clinically and this was probably the most important factor which led to thromboembolism in this case. There was no evidence of any other risk factor being present.

Thirdly, we noted the puzzling case of an active 22 year-old Caucasian girl who collapsed during warm-up for a rugby match. Post-mortem examination revealed extensive PE and occlusive adherent thrombi in the calf veins. She was not overweight or obese and there was no evidence of any genetic abnormality, or any other known risk factor, including a history of VTE or oral contraceptive use. Although the etiologic factors associated with this DVT/PE sequence appeared to be enigmatic, unacknowledged contraceptive use could not be ruled out.

Cardiovascular disease and fatal PE

A 27 year-old Caucasian female known to have congenital tricuspid atresia and right heart failure died from PE after a short episode of atrial fibrillation. Fresh thromboemboli were present in the main pulmonary arteries of both lungs. We hypothesize that the failing heart may have been the source of these emboli. We also encountered another case of PE with heart disease that involved a 39 year-old Maori woman with severe obesity (BMI= 57.09 kg/m^2) and congestive heart failure, who died after developing PE. Post-mortem examination revealed both left atrial and ventricular hypertrophy, with a large fresh thrombus in the left pulmonary artery. We think that this was the result of altered cardiovascular hemodynamics in a pro-thrombotic state induced by obesity. Another case of PE with cardiovascular disease, also associated with obesity (BMI= 36.02 kg/m^2), was encountered in a 38 year-old European woman with ischemic heart disease. The autopsy showed extensive atherosclerosis of the left anterior descending coronary artery with advanced atheroma in the aorta. Thromboemboli were present in the pulmonary arteries of the left lower lobe.

As discussed above, there is mounting evidence that the etiopathogenic mechanisms responsible for DVT/PE and atherosclerosis are inter-related. Clinical studies have shown that patients with VTE have an increased incidence of accelerated atherosclerosis (64). Also, as discussed above, the link between thromboembolism and accelerated atherosclerosis may be further appreciated by the findings of elevated levels of CRP and other related pro-inflammat-

ory cytokines, such as TNF-alpha and IL1, which are manifest in these cases. These in turn lead to the complications of endothelial dysfunction, atheromatous plaque formation and thrombosis.

Post-partum fatal PE

We found only one case of fatal postpartum PE. The patient was a 45 year-old Caucasian female and large thromboemboli were noted in both her right and left pulmonary arteries However, their source was anatomically impossible to identify. Further analysis of this case did not reveal any other well known PE risk factor, history of recurrent VTE, thrombophilias or intake of pro-thrombotic medication.

Several authors have emphasized a strong association between postpartum PE and other pro-thrombotic conditions such as antenatal pulmonary edema, metabolic acidosis, diabetes, protein S deficiency and treatment with ritodrine and betamethasone (65;66). However, pregnancy is associated with all the elements of Virchow's triad, venous stasis, vascular damage, and hypercoagulability (67). Pregnancy related high levels of estrogens and progesterone determine smooth muscle relaxation leading to venodilatation and a decline in venous return from the legs with pooling of blood, favoring thrombogenesis (67-69). In addition, the enlarged gravid uterus increases the vascular stasis by compressing the vessels (67). Also, estrogens stretch the vascular endothelium of the dilated vessels with subsequent rupture, of that layer, and exposure of the subendothelial space to blood flow, resulting in activation of coagulation tissue factors (69). During pregnancy, the anticoagulant activity of protein S is reduced and a procoagulant state is achieved by high levels of fibrinogen and factors V, IX, X, and VIII. In addition, fibrinolysis is decreased as a result of increased activity of PAI-1 and PAI 2. A low activity of t-PA is noted as well (67). We may therefore postulate that the above described molecular dynamics may contribute to the increased risk of DVT/PE during pregnancy.

Oral contraceptives and fatal PE

Over 30 years ago, Sartwell et al (70) postulated that the use of oral contraceptives (OC) is associated with VTE. Thus, it was subsequently shown that the risk of PE is double in women taking OCs compared with non-users (71). Such risk of an OC-related VTE with a fatal event is so very rare (72), thus justifying the continued widespread use of these medications. However, OCs should not be given to patients with: ischemic heart disease, hypertension, atherogenic lipid disorders, focal or crescendo migraine, cigarette smoking, neurological conditions, prothrombotic conditions such as factor V Leiden single-point mutation and obesity (73, 74).

Our single case example in this category was a 36 year-old obese European woman who was also taking a third generation OC containing ethinyl-oestradiol and gestodene (femodene). The important question in these circumstances is which component of the OC cocktail was the most important in promoting PE. Lidegaard et al (75) have reported a fourfold increased risk of VTE in women taking a third generation OC containing gestodene. Thus, gestodene appears to be associated with the production of important abnormalities in the coagulation and fibrinolytic systems, resulting in a significant stimulation of fibrin turnover (76). On the other hand, the oestrogen component also seems to increase the risk of PE in a dose related manner by acting on the vascular endothelium as described above (77). Therefore, we believe that the pro-thrombotic effect of the femodene was the result of the combined action of both gestodene and estradiol.

In addition, she was also a heavy smoker, and it is generally acknowledged that smoking induces a pro-thrombotic state via increased biosynthesis of thromboxane, which in turn stimulates platelet-dependent thrombogenesis (78). Smoking also promotes degenerative changes in the vascular endothelium leading to the formation of atheromas which may fracture

resulting in thrombus formation (79). More recently, Cirillo et al (80) have shown that smoking related nicotine acts on endothelial and smooth muscle cells by initiating a pro-thrombotic state through the induction and promotion of tissue factors.

Postmortem examination of our case also revealed a congested liver with two sub-capsular, multinodular, circumscribed, yellow/brown lesions with central fibrosis. These lesions were consistent with focal fibro-nodular hyperplasia and a hepatocellular adenoma, both of which may have been facilitated by the OC. However, death was the result of a massive PE, as both right and left pulmonary arteries were blocked by thromboemboli. The pathology report concluded that "the massive pulmonary thromboembolism was the result of the simultaneous influence of several risk factors; namely obesity (BMI= 32.9 kg/m^2), femodene ingestion and smoking". Most likely, these acted in concert to induce the above discussed abnormalities of coagulation and fibrinolysis.

Cancer and fatal PE

Two of our subjects were known with cancer. The first was a 37 year-old morbidly obese Maori, who also had primary hyperparathyroidism. Post-mortem examination showed widespread pulmonary emboli and invasive endometrial carcinoma. The second was a 44 year-old Caucasian with known ovarian cancer, who died after a very large thromboembolus had lodged at the bifurcation of her pulmonary artery.

It has been estimated that one of every seven hospitalized cancer patients dies from apparent PE. Remarkably, sixty per cent of all patients who died of massive PE with absence of other readily apparent PE risk factors also showed localized cancer or limited metastatic disease which would have otherwise resulted in prolonged survival in the absence of such lethal pulmonary emboli (81).

A predisposition for thrombosis appears likely in the presence of cancer via several factors. One of these is pre-chemotherapy platelet levels above 350,000/mm^3 (82). Recent studies have demonstrated that pancreatic and lung cancer cells are capable of expressing TF-bearing microparticles (MP) and P-selectin glycoprotein ligand 1 (PSGL-1), which would promote in-vivo a pro-thrombotic state (83). Other studies performed in human astrocytoma cell lines showed that TF is up-regulated by hypoxia via Akt activation and via Ras/MEK/ERK signaling which are also implicated in carcinogenesis. However, TF returns at least partially to normal by induction of PTEN which is usually decreased in high grade astrocytoma/ glioblastomas (84).

Overall, one may regard cancer as a pre-thrombotic state. If other PE risk factors, such as obesity are also present, the chances of developing a fatal episode of PE increase significantly.

Conclusions

In our series of women of reproductive (child-bearing) age, with fatal PE, obesity appears to be the most frequent risk factor. Obesity should be considered an inflammatory state which needs to be therapeutically and prophylactically addressed, since it leads to thromboembolism via the prothrombotic action of adipose tissue hormones and abnormalities in the fibrinolytic and coagulation systems associated with endothelial dysfunction. Based on the information provided by this study, PE should be classified into (fatal) obesity-related (ORPE) and (fatal) non-obesity related (NORPE) pulmonary embolism. The former represents a distinct pathophysiological entity in which from the earliest stage the patient has a higher chance of developing a fatal embolic event since several pro-thrombotic factors are activated. Obese women should be offered a weight reduction program since coagulation and fibrinolytic abnormalities could improve dramatically during such a regimen. In addition, anti-thrombotic prophylactic treatment should be offered as well in these patients. However, these concepts should be further evaluated in large prospective studies.

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