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Short-term exposure to high levels of air pollution as a risk factor for acute isolated pulmonary embolism

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ABSTRACT

Background: The association between air pollution exposure and occurrence of venous thromboembolism is a matter of debate. This retrospective case-control study investigated the associations between one month's exposure to elevated levels of different pollutants (i.e. PM_{10}, CO, NOx, O_3, SO_2, Benzene, Benzoapyrene, Nickel, Lead Arsenic) and the development of acute isolated pulmonary embolism (PE).

Methods: The cases included 33 patients consecutively admitted to Padua Hospital with an objectively proven diagnosis of acute unprovoked (i.e. without predisposing conditions) isolated (i.e. without deep vein thrombosis) PE. The control group consisted of 72 consecutive patients with objectively proven acute provoked (i.e. associated to predisposing conditions) isolated PE. Average mean concentrations of pollutants in the month before PE diagnosis were computed by monitors located at 2 different sites throughout the city of Padua, and were obtained from the Regional Agency for Environmental Protection.

Results: Individuals who had PM_{10}, NOx, Benzene, Benzoapyrene, Cadmium, and Lead exposure equal/above the 2nd tertile, measured in controls, showed a significant increase in the risk of unprovoked PE. In case of PM_{10} and Benzoapyrene this risk was not affected after adjustment for possible confounders. In fact, in the multivariate logistic regression analysis, the OR values were 5.24 (95% CI: 1.52-18.12) for PM_{10} and 3.95 (95% CI: 1.06-14.71) for Benzoapyrene exposure in the month before PE diagnosis.

Conclusions: Our results, although preliminary, identify short-term (i.e. one month) exposure to elevate levels of air pollutants as a possible risk factor for the development of acute isolated PE. Larger studies are needed to confirm our results.

Introduction

Air pollution is composed of a heterogeneous mixture of compounds including ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen oxides (NO_X), liquids, and particulate matter (PM). PM can be of natural or anthropogenic origin and vary in size and composition. Variations in their chemical composition depend not only on their source but also on geographical, local and atmospheric conditions. Particles with an aerodynamic diameter of < 10 μm (PM_{10}), which can penetrate beyond the nasopharyngeal airway, are known as inhalable particles; they include those with a diameter of < 2.5 μm ($PM_{2.5}$ or fine particles), and these in turn include those with a diameter of < 0.1 μm ($PM_{0.1}$ or ultrafine particles) [1–3]. Exposure to inhalable particulates has been associated with increased morbidity and mortality [4]. The most convincing evidence focuses on respiratory and cardiovascular effects (such as myocardial infarction, heart failure and arrhythmias) attributed to short-term (acute transient peaks) and long-term (over many years) exposure to pollution [5,6].

Recently, there has been a growing interest in the effect of air pollution as a possible risk factor for venous thromboembolism (VTE) [7–9], and links between air pollution and arterial and venous thrombosis are currently under investigation. The two main mechanisms involved seem to be: *i*) pro-inflammatory and oxidant effects involving lung epithelial cells and alveolar macrophages [10] and *ii*) activation of the clotting cascade [11–14]. The direct relationship between levels of particulate matter and cardiopulmonary disease on the one hand, and hypercoagulability on the other, suggests the hypothesis of a possible correlation between exposure to fine particulate matter and the onset of acute isolated (i.e. without deep vein thrombosis) pulmonary embolism (PE) due to a potential direct damage to the lung vasculature. The aim of our study was to investigate the role of one month's exposure to elevated levels to a number of ambient outdoor air pollutants (PM_{10}, CO, NOx, O_3, SO_2, Benzene, Benzoapyrene, Nickel, Lead Arsenic) as risk factor for the development of acute isolated PE.

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Patients and Methods

Study population

All patients consecutively admitted to our Thrombosis and Haemostasis Unit at Padua University Hospital between January 2008 and October 2012 with an objectively proven (either by ventilation/perfusion lung scanning [15] or by a spiral computer tomography scan) diagnosis of an acute first episode of isolated PE were considered. Only subjects with a "high probability" of PE at VQ scan were enrolled in the study. As far as CT scan was concerned, the diagnostic criteria for acute PE include the following: *i*) arterial occlusion with failure to enhance the entire lumen due to a large filling defect; *ii*) a partial filling defect surrounded by contrast material; *iii*) a peripheral intraluminal filling defect that forms acute angles with the arterial wall. The protocol in our Unit requires that all patients with PE should undergo compression ultrasound (CUS) of the legs to identify the presence of associated DVT. Cases were considered those individuals with unprovoked (without a predisposing condition) isolated PE meanwhile controls were considered those patients with a provoked (associated to permanent or transient risk factors) isolated PE. On this purpose, study subjects were asked about the presence of associated risk factors for VTE in the month preceding hospital admission (i.e. trauma or surgery, hormonal treatment, pregnancy or puerperium, medical diseases, active cancer). The presence of any heart disease (such as heart failure, myocardial infarction, atrial fibrillation or flutter, and valvular heart disease) lasting at least three months before PE diagnosis was also evaluated [16]. Diagnostic criteria for cardiac diseases were those reported in the European Society of Cardiology Practice Guidelines available at www.escardio.org. Patients were excluded if they were under anticoagulant treatment at the time of the diagnosis of PE, if they were under 18, if they exhibited a previous episode of PE or if they were resident outside the city of Padua. After informed consent, all subjects enrolled underwent thrombophilia screening (panel included antithrombin, protein C and S, lupus-like anticoagulants, factor V Leiden and prothrombin gene mutation) either prior to treatment or at least three weeks after discontinuation according to the methods described elsewhere [17,18].

Air pollution data

We obtained from the Regional Agency for Environmental Protection (Agenzia Regionale per la Protezione Ambientale - ARPA Veneto) average mean concentrations of PM_{10}, CO, NOx, O_3, SO_2, Benzene, Benzoapyrene, Nickel, Lead and Arsenic computed using data from monitors located at 2 different sites throughout the city of Padua. All participants were assigned to one of two geographic areas based on their residence at the time of the study. In order to estimate individual exposure, PM_{10}, CO, NOx, O_3, SO_2, Benzene, Benzoapyrene, Nickel, Lead Arsenic levels were evaluated using ambient concentrations averaged over the month preceding the index date. Index dates were the date of PE diagnosis. The nearest distance between station and the address of each subject enrolled in the study was identified using the Google Maps Distance Calculator program (daftlogic.com). The study population was composed of residents in the City of Padua. Any subjects who had changed their residence during the month before PE diagnosis admission or who had a residence farther than 8 km from the control reference were excluded.

The study was conducted in accordance with the amended Declaration of Helsinki. It was notified to the local Ethic Committee as requested by the protocol of the Padua University-Hospital for retrospective studies.

Statistical analysis

The statistical analysis was performed using a commercially available statistics software package - SPSS 17.0 (SPSS Inc., Chicago, Il, USA). Mean values and standard deviation (SD) were calculated for age and distances from the stations of cases and controls, the difference was assessed by Student's t test. Differences between frequency distribution according to qualitative variables (gender, COPD, smoking status, educational level, season and temperature) were calculated using Chi-square test. To allow comparison across pollutants, the monthly PM_{10}, CO, NOx, O_3, SO_2, Benzene, Benzoapyrene, Nickel, Lead Arsenic concentrations were divided into tertiles and frequencies of cases and controls were compared using Chi-square test. The risk of unprovoked isolated PE due to high levels of pollutants was evaluated by setting the 2nd tertile of each pollutants levels in the control group as cut-off points and calculating the odds ratio (OR) and the 95% confidence interval (CI) for cases as compared to controls. To adjust for possible confounders, a logistic regression model was used taking into account age, gender, COPD, smoking status, educational level, distance from monitor stations, season and temperature. All tests for statistical significance were two-tailed and p values below 0.05 were considered statistically significant.

Results

Out of 120 patients consecutively admitted to our hospital during the study period with the diagnosis of acute isolated PE, 15 were excluded (6 were resident outside the city of Padua or at distance ≥ 8 km from the nearest monitor station, 4 were under anticoagulant treatment before hospitalization, 4 had experienced a previous episode of PE and one was under 18). Of the remaining 105 patients, 33 (31%) were subjects with unprovoked PE (cases) and 72 (69%) were individuals with provoked PE (controls). PE was diagnosed by CT scan in the great majority (87.2%) of the study patients. Moreover, the proportion of patients with small subsegmental PE was low both in cases (18.3%) and in controls (22.5%). The main demographic, clinical and exposure characteristics of the study population are shown in Table 1. There was weak evidence against the null hypothesis that males and females were equally represented ($p = 0.07$). No statistically significant difference in age ($p = 0.93$), COPD and smoking history ($p = 0.92$ and $p = 0.63$, respectively), educational level ($p = 0.68$), and mean temperature

Table 1
Demographic, clinical and exposure characteristics of the study population.

	Unprovoked	Provoked	p value
No. of patients	33	72	-
Sex, M/F	7/26	28/44	0.07
Age, mean ± SD (range)	67 ± 18 (24-95)	68 ± 17 (22-89)	0.93
COPD history	3 (9)	7 (10)	0.92
Smoking history			
Never	20 (61)	40 (56)	0.63§
Ex	11	26	
Current	2	6	
Education			
Elementary/middle school	22 (67)	45 (63)	0.68°
High school	7	16	
College	4	11	
Distance from monitor stations, Km			
Station 1	4.3 ± 1.8	4.5 ± 2.4	0.64
Station 2	5.1 ± 2.3	6.4 ± 1.8	0.10
Season			
November-February	17 (52)	21 (29)	0.03^
March-June	7	30	
July-October	9	21	
Mean temperature, °C			
-4.0 to 7.0	14 (42)	24 (33)	0.93*
7.1 to 18.1	12	24	
18.2 to 29.5	7	24	

Unless otherwise indicated, the numbers in brackets indicate a percentage.
COPD: Chronic obstructive pulmonary disease.
§never vs previous and current; °elementary/middle school vs high school and college; ^November-February vs March-June and July-October; *-4.0 to 7.0 vs 7.1 to 18.1 and 18.2 to 29.5.

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(p = 0.93) was observed between cases and controls. According to season, a significant higher prevalence of diagnosis was observed in cases in the period between November and February than that observed in controls (52 vs 21%, p 0.03). The most relevant predisposing conditions observed in controls were: *i*) Thrombophilia (31%), *ii*) Active cancer (24%), Heart diseases (18%), and *iv*) Recent trauma or surgery (17%) (Table 2). Twelve controls presented with more than one predisposing condition. Table 3 shows the tertiles of the average of the air pollutants level measured in the area of residence during the month before the date of PE diagnosis. As for PM10, NOx, Benzene, Benzoapyrene, Cadmium, and Lead a significant higher prevalence of cases in the 3th tertile than in controls was observed. As for CO, O_3, SO_2, Nickel, and Arsenic no statistically difference between cases and controls was found. Stratifying the levels of the pollutants according to the season of the diagnosis of PE the monitor stations registered, considering the overall study population, a higher median concentration of pollutants during the period between November and February than in the rest of the year (data not shown). No significant difference in the median values of air pollutants levels between station 1 and station 2 was registered (data not shown). Using the upper limit of the 2nd tertile measured in controls in the month before PE diagnosis as a cut-off point, we found a significant increase in the risk of unprovoked PE for individuals who had PM_{10}, NOx, Benzene, Benzoapyrene, Cadmium, and Lead exposure equal/above the cut-off point compared to individuals with exposure below this value (Table 4). In case of PM_{10} and Benzoapyrene this risk was not affected after adjustment for age, gender, COPD, smoking status, educational level, distance from monitor stations, season and temperature. In fact, in the multivariate logistic regression analysis, the OR values were 5.24 (95% CI: 1.52-18.12) for PM_{10} and 3.95 (95% CI: 1.06-14.71) for Benzoapyrene exposure in the month before PE diagnosis (Table 4).

Table 3
Tertiles of exposure to air pollutants of the study population during the month before enrolment.

	Tertiles	No. of Cases (%)	No. Of Controls (%)	p value
PM_{10}, μg/m^3	≤29	7	24	
	30 - 52	4	24	
	≥53	22 (67)	24 (33)	0.001
CO, mg/m^3	≤0.36	5	24	
	0.37 - 0.69	12	24	
	≥0.70	16 (49)	24 (33)	0.14
NOx, mcg/m^3	≤50	6	24	
	51 – 123	8	24	
	≥124	19 (58)	24 (33)	0.02
O_3, mcg/m^3	≤41	14	24	
	42 – 72	12	24	
	≥73	7 (21)	24 (33)	0.20
SO_2, mcg/m^3	≤1.00	7	24	
	1.01 - 2.00	17	24	
	≥2.01	9 (27)	24 (33)	0.53
Benzene, mcg/m^3	≤1.15	7	24	
	1.16 - 3.35	6	24	
	≥3.36	20 (61)	24 (33)	0.01
Benzoapyrene, ng/m^3	≤1.00	6	24	
	1.01 - 2.00	6	24	
	≥2.01	21 (64)	24 (33)	0.004
Cadmium, ng/m^3	≤0.36	5	24	
	0.37 - 0.75	10	24	
	≥0.76	18 (55)	24 (33)	0.04
Nickel, ng/m^3	≤2.86	10	24	
	2.87 - 4.64	13	24	
	≥4.65	10 (30)	24 (33)	0.76
Lead, ng/m^3	≤8	5	24	
	9 – 14	10	24	
	≥15	18 (55)	24 (33)	0.04
Arsenic, ng/m^3	≤0.50	9	24	
	0.51 - 1.24	9	24	
	≥1.25	15 (46)	24 (33)	0.23

Discussion

Our results show that the short-term (i.e. during the month before PE diagnosis) exposure to elevated levels of PM_{10}, NOx, Benzene, Benzoapyrene, Cadmium, and Lead is a possible risk factor for unprovoked acute isolated PE. In particular, exposure to PM_{10} and Benzoapyrene is characterized by a 4 to 5-fold independently increase in the risk of isolated PE for the time exposure of one month before acute diagnosis. Although the differences were statistically significant compared to subjects with provoked PE, the confidence intervals are quite wide, which is possibly due to the relatively small number of individuals enrolled in the study.

As far as the possible pathogenic effects of PM_{10} on VTE, our data are in agreement with those in previous publications [19,20]. The novelty of our study lies in the possible role of Benzopyrene in determining the risk of VTE. Benzo[a]pyrene is one of the two isomeric species of benzopyrene; the other, less common type, is benzo[e]pyrene. They both belong to the chemical class of polycyclic aromatic hydrocarbons and the main atmospheric sources are residential wood burning, coal tar, automobile exhaust fumes (especially from diesel engines) and in all smoke resulting from the combustion of organic material [21]. The link between benzoapyrene and cancers has been well documented [22]. On the contrary, to the best of our knowledge, no study published so far has investigated the association between increased levels of benzoapyrene and the risk of VTE.

The finding of higher levels of pollutants in the cases compared with the controls, observed in our study, does not depend on different areas of residence. In fact, we did not find any difference between levels of air pollution recorded by the monitor station 1 and 2. The observed

Table 2
Predisposing conditions in patients with provoked PE.

Predisposing conditions	N. of patients (%)
Thrombophilia	26 (31)
Factor V Leiden	12
Prothrombin mutation	6
PC/PS/AT defect	4
Lupus-like anticoagulants	4
Active cancer	20 (24)
Heart diseases	15 (18)
Heart failure	5
Atrial fibrillation or flutter	4
Myocardial infarction	3
Valvular heart disease	3
Recent trauma or surgery	14 (17)
Medical diseases	7 (8)
Hormonal treatment, pregnancy or puerperium	2 (2)

PC: protein C; PS: protein S; AT atithrombin.

Table 4
Estimated Odds Ratio for isolated PE associated with an exposure to elevated air pollutants.

	2nd Tertile	ODDS RATIO (95% CI)	
		Univariate	Multivariate
PM_{10}, μg/m^3	53	4.00 (1.65-9.59)	5.24 (1.52-18.12)
CO, mg/m^3	0.7	2.13 (0.92-4.93)	1.51 (0.42-5.41)
NOx, mcg/m^3	124	2.55 (1.10-5.93)	2.35 (0.76-7.25)
O_3, mcg/m^3	73	0.54 (0.20-1.42)	0.83 (0.26-2.70)
SO_2, mcg/m^3	2.01	1.43 (0.63-3.29)	0.78 (0.27-2.24)
Benzene, mcg/m^3	3.36	2.71 (1.16-6.33)	3.05 (0.88-10.62)
Benzoapyrene, ng/m^3	1.89	3.50 (1.48-8.29)	3.95 (1.06-14.71)
Cadmium, ng/m^3	0.76	2.40 (1.03-5.57)	2.19 (0.77-6.21)
Nickel, ng/m^3	4.65	1.07 (0.45-2.54)	0.60 (0.22-1.64)
Lead, ng/m^3	15	2.72 (1.17-6.35)	2.87 (0.83-9.91)
Arsenic, ng/m^3	1.25	1.67 (0.73-3.83)	1.12 (0.40-3.16)

Multivariate analysis was adjusted for age, gender, COPD, smoking status, educational level, distance from monitor stations, season and temperature.

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difference rather depends on the season in which embolism occurred. In the group of cases have occurred in fact more episodes from November to February, a period of increased air pollution. As far as the seasonal variability is concerned, the results of our study are in agreement with previous studies [23,24] conducted in Northern Italy which have identified a seasonal variation in the development of thromboembolic events. In particular, a higher incidence of PE/DVT was reported in winter than in the rest of the year. As suggested in the hypothesis put forward by Dentali et al. [24], our data confirm that exposure to higher levels of air pollutants during winter is associated with a higher incidence of thromboembolic events.

Long-term exposure to particulate air pollution has been associated with increased risk of coronary artery disease and cerebrovascular disease in multiple investigations conducted in several countries [1]. In particular, inhalation of particulate matter leads to pulmonary inflammation with secondary systemic effects or, after translocation from the lung into the circulation, to direct toxic cardiovascular effects. Through the induction of cellular oxidative stress and proinflammatory pathways, particulate matter augments the development and progression of atherosclerosis via detrimental effects on platelets, vascular tissue, and the myocardium. These effects seem to underpin the atherothrombotic consequences of acute and chronic exposure to air pollution [25]. Again, Baccarelli et al. [7,8] found evidences in support of an association between long-term exposure to particulate air pollution and risk of DVT due to an increased prothrombotic state. In contrast, PE has received little attention in studies on the cardiovascular outcomes of air pollution. In a time-series analysis from the Netherlands, Hoek et al. [26] reported an association between short-term exposure to ambient ozone and, to lesser extent, to black smoke and PM_{10}, and increased mortality from a broad category of thromboembolic events including arterial and venous accidents in various sites. To date, no study has specifically addressed the association between particulate air pollution and isolated PE. Two different etiopathogenetic mechanisms might cause isolated PE (PE in the absence of DVT) in subjects exposed to elevated levels of pollutants. The first may be an "in situ" pulmonary thrombosis due to a potentially higher particulate matter prothrombotic effect on the pulmonary artery than in other systemic blood vessels. In this context, a speculative model could be derived from animals in which intratracheal instillation of ultrafine polystyrene particles increased the risk of in situ thrombus formation [27]. The other possible concurrent mechanism could be due to heart diseases related to exposure to high pollutants levels, which could subsequently be associated with the development of pulmonary embolism in the absence of DVT, as has been demonstrated [16,20]. The few studies that reported results for gaseous pollutants and cardiovascular outcomes [6,28,29] observed a positive association between NO_2, O_3, and SO_2 levels and cardiac diseases. In a multifactorial model of diseases it is possible that air pollution can provide a "final push" able to trigger thromboembolic complications in patients with a preexisting prothrombotic condition (i.e. cancer). However, to address this issue it would be necessary to conduct studies in other patients, for example in those with cancer (or with other predisposing conditions) with and without pulmonary embolism in order to evaluate the addictive effect, if any, of air pollution on provoked PE.

As far as "exposure time" is concerned the month before the thrombotic event was considered. The idea behind this choice is that slightly higher levels of exposure to pollutants for a longer period of time may equal exposure to very high levels for a shorter time. In fact, we do not hypothesize a significantly higher exposure in cases than in controls for a short period of time (i.e. a week) but a small difference in exposition levels lasting for a longer period of time (i.e. one month). Notably, in a preliminary analysis of our database the role of one week's exposure was evaluated (data not shown) and no statistically significant difference was found between cases and controls as far as the levels of pollutants were concern. Moreover, no significant increase risk of unprovoked isolate PE was observed for each single pollutant considered in our study.

Our study has several limitations. Firstly, there is a relatively small sample size which can affect the precision of our estimates. In particular, the wide range of the 95% confidence intervals gives little confidence in the precision of our point estimation. Furthermore, because of the number of variables included in the logistic regression analysis it must be noted that the specific weight of each of these is questionable. Secondly, and more importantly, the evaluation of the environmental air pollution was used as a surrogate measurement, which may have resulted in an underestimation (more likely) or overestimation of the real personal exposure for each patient. However, in contrast to the population-based study in which data are obtained from a medical database, the careful and direct collection of demographic and clinical data from the subjects in our study possibly allowed a more precise correlation with the air pollution exposure. As for the measurement error due to the use of regional stations for exposure assessment, it can be regarded as a common weakness shared by all studies of this type. The distance of the subject's residence from the monitoring station does not fully take into account individual differences in the time spent at home and in other environments, such as workplaces or in traffic while commuting. Thirdly, data on PM2.5 levels were not available. Thus, the role of PM2.5 in the development of isolated unprovoked PE is unknown. Notably, recent studies empathized the particular role of the levels of PM10 in determining the risk of thrombosis [19,20]. Fourthly, we are fully aware that the relatively small sample size considered in our study could have generated misclassifications and bias which can undermine our conclusions. Nevertheless, consecutive patients, enrolled in 4 years' time, were selected with an objectively proven diagnosis of PE, living at a relatively short distance from monitor stations. Fifthly, information on specific sources of pollution (i.e. factories, major traffic roads, etc.) close to the patient's home was not included in this study. It must be noted, however, that there can be general limitations in all the studies that measure the exposure to air pollution indirectly (including distance from major roads). Ideally, cases and controls should wear a personal dosimeter for direct evaluation of exposure but this is obviously not feasible in a study like ours.

In conclusion, our results, although preliminary, identify short-term (i.e. one month) exposure to elevate levels of air pollutants as a possible risk factor for the development of acute isolated PE. At present, it is only possible to hypothesize that air pollution may be involved in the generation of in-situ thrombosis in the pulmonary artery. Larger prospective multicentre investigations are needed to confirm this finding and clarify the potential underlying mechanisms.

Conflicts of Interest

None to declare.

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