

Argentine Registry of Venous Thromboembolism

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ABSTRACT

Background

Venous thromboembolism (VTE) with its two presentations: deep vein thrombosis (DVT) and pulmonary embolism (PE) is the third leading cause of cardiovascular morbidity and mortality. To obtain national data on this pathology, the Council of Cardiovascular Emergencies and the Research Area of the Argentine Society of Cardiology conducted a prospective registry of patients with confirmed VTE in 54 centers during one year.

Methods

Patients with confirmed VTE were included in a prospective, consecutive and continuous registry during 2009-2010 in 54 participating centers of the Autonomous City of Buenos Aires and the rest of the country (n = 26 and 28, respectively). Individual patient data were registered in an electronic form.

Results

One hundred and eighty one patients with median age of 66 years (53-79), 59% of which were women, were included in the study. Pulmonary embolism was diagnosed in 34%, DVT in 33% and PE + DVT in 33%. The most prevalent risk factors were prolonged rest in 42% of cases, cancer in 20%, history of VTE in 10% and none in 9%. All DVT were diagnosed by venous Doppler. Pulmonary embolism was diagnosed by spiral CT scan (86%), ventilation/perfusion scintigraphy (16%) and arteriography (0.8%). Seventy percent of patients received low molecular weight heparin, 40% unfractionated heparin, 11% thrombolytic agents and 10% had no treatment. Vena cava filter was used in 12% of cases and mechanical ventilation in 9%. Recurrent PE was observed in 4% of patients, shock in 14% and in-hospital mortality was 7%.

Conclusions

Prolonged rest was the most prevalent risk factor. Only 9% of patients showed no known risk factors. Helical CT scan was the preferred method for PE diagnosis. Low molecular weight heparin was the treatment of choice for VTE. Thrombolytics were used in 11% of PE patients and vena cava filter in 12% of VTE patients. VTE in-hospital mortality was 7%.

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Key words

> Registry - Venous Thromboembolism

Abbreviations

>	ABNP	Brain natriuretic peptide	RBBB	Right bundle branch block
	CT	Computed tomography	PE	Pulmonary embolism
	DVT	Deep vein thrombosis	PF	Predisposing factors
	ECG	Electrocardiogram	VTE	Venous thromboembolism

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are the two forms of presentation of venous thromboembolism (VTE), a common and highly mortal condition if not diagnosed and treated properly. (1) In the United States about 600000 cases are diagnosed annually, with almost 10% mortality even with treat-

ment. It is the leading cause of cardiovascular death in hospitalized patients (2, 3) and the third cause of cardiovascular morbidity after ischemic heart disease and stroke in the general population. (4)

According to reports, up to 50% of DVTs diagnosed by phlebography may present with PE in their evolution (5) and patients with PE who are diagnosed with

DVT are at greater morbidity and mortality risk. (6) It is then imperative to use preventive treatments in patients hospitalized for other reasons with risk factors for developing DVT. (7)

Signs and symptoms of PE are common to other conditions, presenting variable intensity, and in some cases non-specificity. (8) Thus, complementary methods, based on clinical suspicion are essential for diagnosis. (9)

Different international registries (10-20) have provided clinical information about the disease, but there is no local information of VTE. In order to know the reality concerning this disease in our country, the Emergency Cardiovascular Council and the Research Area of the Argentine Society of Cardiology (SAC) have performed the first Argentine Registry of Venous Thromboembolism.

METHODS

Patients with prospectively confirmed VTE diagnosis from 54 participating centers in the Autonomous City of Buenos Aires and the rest of the country were prospectively, continuously and consecutively included in the registry during 2009-2010. Venous thromboembolism was diagnosed in each center according to classical lower limb ultrasound criteria in the case of probable deep vein thrombosis (DVT) or by spiral computed tomography, radioisotope scintigraphy or pulmonary angiography in cases of suspected PE. Follow-up was limited to hospital stay. The registry form was designed in electronic format (pdf) available at SAC's website, and once completed was submitted to SAC's coordinating center via e-mail. To preserve data confidentiality, patients were identified by an exclusive registry number for each center and a patient number. Data were assessed at regular intervals, and contact between the coordinator and the principal investigator at a specific center was scheduled to solve inconsistencies. The registry form included age, gender, predisposing factors (PF), clinical presentation, diagnostic methods, treatments and in-hospital adverse events. Prolonged rest was defined as that lasting ≥ 48 hours and in-hospital mortality as that occurring during hospitalization, regardless the cause.

Statistical analyses

Data submitted by each center were incorporated into a unique database and analyzed using EPI info 2000 and SPSS software, version 13 for Windows (September 1, 2004, IL, USA). Categorical variables were expressed as percentages and analyzed using the chi-square test (with Yates correction if applicable) or Fisher's exact test. Quantitative variables were expressed as mean \pm standard deviation or median with interquartile range (25-75%), and were analyzed using the t test or the Wilcoxon test, as appropriate. A p value < 0.05 was considered statistically significant. Odds ratio (OR) and its 95% confidence interval (95% CI) was used to express superiority. A stepwise logistic regression analysis was performed to identify variables independently associated with in-hospital mortality. A two-tailed p value < 0.05 was considered statistically significant. The registry was approved by the Ethics Committee of the Argentine Society of Cardiology.

RESULTS

A total of 181 patients, 62 (34.3%) with PE, 60 (33.1%) with DVT and 59 (33.6%) with both diseases were included in the study. Median age was 66 years (53-79

years). Fifty-one percent of patients were older than 70 years and 59% were women. The most common predisposing factor was prolonged rest in 42% of cases, followed by cancer (20%), previous history of thromboembolism (10%), and no identified risk factor in 9% of patients (Table 1). Predisposing factors were common for both forms of VTE presentation (Figure 1).

From the 119 patients in the DVT registry, 65% were hospitalized for suspected DVT/PE, 22% for clinical pathologies, 5% for surgeries, 2% for neurological pathology and 6% for other causes. All the cases were diagnosed by venous Doppler, 80% in the first 48 hours after hospitalization, regardless the cause of admission. The remaining 20% was diagnosed in patients with more than 72-hour hospitalization for other pathologies, despite 70% of cases had received correct prophylaxis. Lower limb asymmetry and edema were manifest in 80% of DVT cases.

Patients presenting only DVT (n = 60) were mostly hospitalized in a hospital floor (60%), while 80% of PE patients were hospitalized in intensive care [Coronary Care Unit (90%), and Intensive Care Unit (10%)] and 20% in a general ward.

From the 121 PE patients, 62% were admitted to the hospital for suspected VTE and in the remaining patients, VTE occurred during hospital stay due to another illness: medical (21%), traumatological (6%), surgical (4%), neurological (2%) and "other" (5%).

Dyspnea was the most frequent symptom in PE patients (88%) (Table 2).

ECG was normal in 47.7% of PE patients and pathological in the remaining 52.6%. Among these findings, 31.6% of cases presented S1-Q3-T3 pattern, 25% evolving negative T waves from V1 to V4, 20% new RBBB, 22% shift from left to right axis deviation and 11.4% atrial flutter or fibrillation.

Chest X-ray was performed in 97% of cases. Less than 10% of patients had radiological signs suggestive of PE, 10% presented unilateral pleural effusion, 7% amputation of the pulmonary artery, 4% oligaemia and 3% an image compatible with pulmonary infarction.

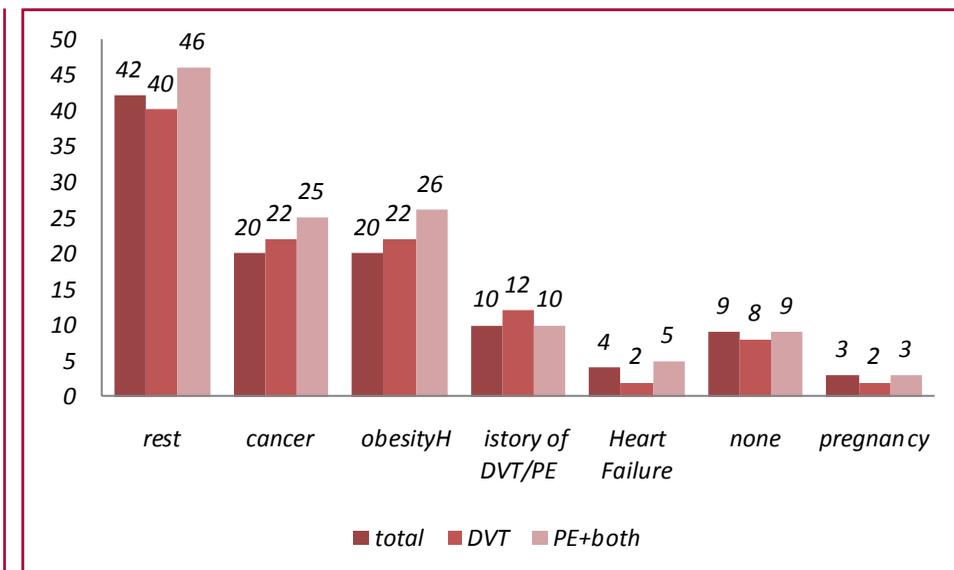
Troponin (T in 71% of cases) was assessed in 76 patients (48%) and was positive in 26% of cases. Sixty

Table 1. Predisposing factors for venous thromboembolism (n = 181)

	n	%
Prolonged rest	76	42
Cancer	36	20
History of VTE	18	10
None	16	9
Heart failure	7	4
Obesity	36	20
Varices	32	18
Pregnancy/puerperium	5	3

VTE: Venous thromboembolism.

Fig. 1. Predisposing factors according to the type of venous thromboembolism.



percent of hypotensive patients and 32% of patients with right ventricular dysfunction had elevated troponin. BNP was measured in 22 patients and was increased in 90% of cases [median 914 µg/dl (320-2018)].

Doppler echocardiogram performed in 118 patients showed normal results only in 23% of cases. Among the most frequent findings, 68% presented right chamber dilation (in half of these patients associated with right ventricular systolic dysfunction), 26.5% paradoxical septal motion and 75% tricuspid regurgitation. Median pulmonary artery systolic pressure was 55 mm Hg (44-61), with >40 mm Hg in 80% of cases.

Imaging diagnostic methods are detailed in Table 3.

Following the classical definition, pulmonary embolism was classified as mild in 34% of cases, submassive in 56% and massive in the remaining 10%. (21)

The most common treatment was low molecular weight heparin (70% of cases) followed by unfractionated heparin (40%), and thrombolytics in 11% of patients. A vena cava filter was placed in 12% of patients. Ten percent of cases did not receive any treatment

In-hospital outcome

Nine percent of the patients required mechanical res-

piratory assistance, 6% were in shock at admission, and this percentage increased to 14% during hospitalization. Recurrence of pulmonary embolism was found in 4% of cases. From the 14 thrombolized patients, 11 had hemodynamic and clinical improvement and 3 died.

Overall in-hospital mortality was 7%, in half of the cases due to embolic recurrence.

Mortality rate in patients with mild PE was 2%, with submassive PE, 9% and with massive PE, 33% (p<0.002). Univariate analysis showed that variables associated with in-hospital mortality were: tachypnea (OR 6; 95% CI 1.8-19; p = 0.0001), hypotension (OR 5; 95% CI 1.5-21; p = 0.04), oligoemia in the chest X-ray (OR 9.5; 95% CI 1.4-63; p = 0.005), and shock (OR 22; 95% CI 6-70; p = 0.0001). Logistic regression in the multivariate analysis revealed that shock was the only variable associated with in-hospital mortality (OR 16; 95% CI 2-66; p = 0.0002)

DISCUSSION

VTE is the third leading cause of cardiovascular mortality after coronary heart disease and stroke. (4) A reasonable clinical suspicion and the use of specific diagnostic methods are required for its diagnosis. The overall incidence in our country is unknown. Population information currently available is based on multicenter registries from the United States and Europe, including heterogeneous populations which, according to random sampling, may be comparable or not to

Table 2. Clinical symptoms of pulmonary embolism

	n	%
Dyspnea	106	88
Tachypnea	37	31
Palpitations	25	20
Chest pain	34	28
Anxiety	11	9
Fever	11	9
Syncope	6	5

Table 3. Diagnostic methods

	n	%
Spiral computed tomography	104	86
Pulmonary scintigraphy	19	16
Pulmonary angiography	1	0,8

that of our country. (10-20) Brazil (10) and Colombia (11) are the only Latin American countries that have performed registries and the present VTE registry is the first one conducted in our country.

Mean age of presentation in our study population was 66 years, the same as in the Spanish Registry (RIETE), (14) similar to the Colombian registry (65 years), (11) higher than that observed in the ICOPER (62.3 years) (15), MASTER (59 years) (18) and Jasper (60 years) (16) registries and lower than that in the Brazilian registry (68.9 years). (10) The age difference seems related to the type of population analyzed.

The higher prevalence of women in our study (59.7%) was also observed in the Colombian registry (66%) and in the ICOPER registry (50%). While the use of contraceptives and postmenopausal hormone replacement therapy have been associated with increased VTE in women, epidemiological data in different registries are not consistent with any difference in the incidence of VTE between men and women. (22). Women predominance in our registry appears to be related to chance.

Regarding the presence of classically described PF, (23) prolonged rest was the most common with a frequency ranging between 30% and 47%, followed by cancer and history of VTE, with similar results than other available registries. (10-18) In 1 out of 10 patients no PF was found. In the ICOPER the frequency of "idiopathic" or primary PE was 20% (15) and in the MASTER (18) REMATEV (17) and Japanese (16) registries it reached 50%. In some registries (10-12, 14) the incidence of VTE patients without PF is not reported. Likewise, the fact that there is variability in the incidence of idiopathic PE could be related to the fact that not all registries show the same PF or perhaps VTE is the first manifestation of an underlying disease (cancer, thrombophilia, among others).

The clinical presentation of our PE patients was similar to that reported by other records, with dyspnea, tachypnea, and chest pain as the most common symptoms. Tachycardia has been reported in 25% to 45% of cases and fever in 9% to 15% in all registries. Syncope and shock are rare. (18) As only cases with confirmed diagnosis of thromboembolic disease were registered, we could not determine the number of patients who were in shock or cardiac arrest and who did not survive in order to make an accurate diagnosis.

ECG was the most common complementary method used and was abnormal in half of the cases. The most frequent finding was sinus tachycardia, as in the PIOPED study. (8) The pattern S1-Q3-T3 was present in 1 out of 3 patients while the presence of negative T and acute RBBB occurred in 1 out of 4 patients, similar to other registries. (10, 17) The incidence of these electrocardiographic patterns of acute cor pulmonale may depend on the percentage of patients with massive PE included in different registries.

Chest radiography in PE is of little value, as demonstrated with the 2322 patients of the ICOPER

study, (24) since it was abnormal in 75% of cases but with very nonspecific findings, the most common being enlarged cardiac silhouette in 27% of cases, pleural effusion in 23%, elevated hemidiaphragm in 20%, increased pulmonary artery in 19% and atelectasis in 18%. Only 8% presented oligoemia and 5% lung infarction as more specific signs. In our registry, 7% of patients had amputation of the pulmonary artery, 4% oligoemia and 3% an image compatible with pulmonary infarction.

Doppler echocardiography is an essential complementary method in patients with PE. The presence of right chamber dilation and/or dysfunction in patients in shock almost certifies the diagnosis of massive PE and in patients without hemodynamic decompensation it allows discriminating between low and moderate risk. (25-27) In our registry, right chamber dilation was the most common finding, present in 68% of cases and in 100% of patients with shock. In the French registry (17) it was found in 64% of cases and in the Polish registry (12) in 76%. Right ventricular hypokinesia was evident in 46% of echocardiograms. In the ICOPER substudy of normotensive patients (28) it was present in 40%, and in 8.4% of our patients with signs of right chamber dysfunction, it was accompanied by shock. The mortality of patients with dilated and/or right ventricular dysfunction was 11% and 5% in patients without right ventricular involvement ($p = ns$). The variability of right ventricular involvement is also related to the type of population analyzed according to the clinical VTE presentation.

Troponin was determined in half of the cases, with a positive result in 1 out of 4 patients and with a direct correlation with the most severe forms of presentation.

Diagnostic methods

Perhaps this is where the main differences between registries are found. In ours, as in the Polish (12) or Brazilian (10) registries, spiral computed tomography (CT) was the most common diagnostic method, while in the ICOPER (15) it was not used and in the JASPER (16) it was scarcely used (14%). The analyses of the National Spanish and RIETE registries, (29) show that use of spiral CT steadily increased since the introduction of the method for clinical evaluation, from less than 20% in 1999 to 70% in 2004 and today is even higher. Concomitantly, radionuclide ventilation/perfusion scanning, which was the diagnostic method that prevailed until 2002/2003, has decreased. This temporal trend seems to account for the different use of the available methodology in the different registries.

Although pulmonary angiography was part of the standard practice in the diagnosis of PE in the sixties, (27) with the advent of spiral CT its implementation is less necessary; generally limiting its use to define doubtful cases. In our study it was used in 0.8% of cases, which is consistent with other existing registries. (11, 14, 18)

Treatment

The use of low molecular weight heparin exceeded that of unfractionated heparin, because of its simple application and no need of frequent laboratory controls. (30) This fact is observed in all contemporary registries. (14, 18) Use of thrombolytics was 11%. Mechanical embolectomy was performed in a single patient due to shock. Vena cava filter was required in 12% (n = 14) of patients with PE, in 10 patients as a result of contraindication for anticoagulation therapy and in 4 patients for "other" causes.

In-hospital outcome

Over 80% of patients had good outcome, remaining stable until discharge. Nine percent required mechanical ventilation and 14% presented with shock during hospitalization (6% at admission). In-hospital mortality of patients with PE was 9%. In the other registries it varies between 6% (REMATEV) and 14% (Japanese and Colombian). This difference between registries may be accounted by the different percentage of PE over DVT (50% PE in the REMATEV registry and 100% in the JASPER and the Colombian registries), the incidence of shock, and the clinical or surgical and inpatient or outpatient conditions.

The overall mortality of patients with VTE was 7%. Preliminary results of the Italian registry IPER, (20) so far with 900 patients, also shows an in-hospital mortality of 7%, which reaches 25% in high-risk PE, 5% in intermediate risk PE and 0.5% in low risk PE according to risk stratification proposed by the European guideline. (22)

Limitations

This is a registry of confirmed VTE related to the Argentina Society of Cardiology and mostly performed by cardiologists. Since 90% of patients with PE were admitted to Coronary Care Units, we cannot generalize our data regarding diagnostic methods, outcome and treatments to those that might be performed in other specialties.

CONCLUSIONS

This is the first Argentine VTE record that provides us with the possibility of getting acquainted with our own data concerning the clinical features, diagnostic methods, treatment and in-hospital outcome of an uncommon and potentially fatal disease.

RESUMEN

Registro Argentino de Enfermedad Tromboembólica Venosa

Introducción

La trombosis venosa profunda (TVP) y la tromboembolia de pulmón (TEP) son las dos formas de presentación de la enfermedad tromboembólica venosa (ETEVE), que constituye la tercera causa de morbimortalidad cardiovascular. Con el objetivo de obtener datos nacionales sobre esta patología, el Consejo de Emergencias Cardiovasculares y el Área de Inves-

tigación de la Sociedad Argentina de Cardiología realizaron este registro prospectivo de pacientes con ETEVE confirmada, en el que participaron 54 centros durante un año.

Material y métodos

El registro incluyó pacientes con diagnóstico confirmado de ETEVE en forma prospectiva, continua y consecutiva durante el período 2009-2010 en los 54 centros participantes de Capital Federal e Interior del país (n = 26 y 28, respectivamente) y cuyos datos individuales se registraron en una ficha con formato electrónico.

Resultados

Se incluyeron 181 pacientes con una mediana de edad de 66 años (53-79); el 59% eran mujeres. Se diagnosticó TEP en el 34%, TVP en el 33% y TEP + TVP en el 33%. Los factores de riesgo más prevalentes fueron: reposo prolongado en el 42%, cáncer en el 20%, antecedentes de ETEVE en el 10% y ninguno en el 9%. Todas las TVP se diagnosticaron por Doppler venoso. El diagnóstico de TEP se realizó por tomografía helicoidal (86%), centellograma de ventilación/perfusión (16%) y arteriografía (0,8%). El 70% recibió heparina de bajo peso molecular, el 40% heparina no fraccionada, el 11% trombolíticos y el 10% no recibió tratamiento. Se empleó filtro de la vena cava en el 12% de casos y asistencia respiratoria mecánica en el 9%. Se observó TEP recurrente en el 4%, shock en el 14% y la mortalidad hospitalaria fue del 7%.

Conclusiones

El reposo prolongado fue el factor de riesgo más prevalente. Solo el 9% no evidenció factores de riesgo conocidos. La tomografía helicoidal fue el método más utilizado para el diagnóstico de TEP. La heparina de bajo peso molecular fue el tratamiento de elección de la ETEVE. Los trombolíticos se emplearon en el 11% de las TEP y el filtro de la vena cava en el 12% de las ETEVE. La mortalidad hospitalaria de la ETEVE fue del 7%.

Palabras clave > Registro - Tromboembolia venosa

Conflicts of interest

None declared.

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PARTICIPATING CENTERS

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