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Clinical research

Prevalence and risk of pulmonary embolism in patients with intracardiac thrombosis: a population-based study of 23 796 consecutive autopsies

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Aims While right intracardiac thrombosis (IT) is a potential cause of pulmonary embolism (PE) similar to that of stroke in left-sided IT, its prevalence and prognostic significance has not been studied in the general population. The aim of this study was to assess the age- and gender-specific prevalence of IT and its relation to PE in a population-based autopsy cohort.

Methods and Results Between 1970 and 1982, 23 796 autopsies, representing 84% of all in-hospital deaths in the Malmö city population, were performed, using a standardized procedure. The relationship between IT and PE was evaluated by cohort analyses and nested case–control studies. IT was present in 1706 (7.2%) patients, 727 and 747 of whom had right and left atrial IT, respectively. PE prevalence in patients with isolated left IT, isolated right IT, and combined IT was 28.5, 35.6, and 48.9%, with RR (95% CI) of 1.5 (1.3–1.8), 2.0 (1.6–2.5), and 3.5 (2.7–4.7), respectively, compared with age- and gender-matched controls. Patients dying from ischaemic heart disease had a 3.2 (2.7–3.6) times higher risk of right IT, which was associated with 43% PE prevalence. Of all patients with PE at autopsy, right IT was found in 354 (6.5%), and the only detected source of PE in 220 (4.0%).

Conclusion Right cardiac thrombosis, though difficult to assess clinically, is as common as left cardiac thrombosis and is associated with an increased risk of PE. The diagnosis should be considered in all cases of PE, especially in patients with atrial fibrillation or myocardial infarction and in the absence of confirmed deep vein thrombosis.

Introduction

Compared with the well-recognized association between left atrial (LA) thrombosis and embolic stroke, typically found in atrial fibrillation patients,[1–3] the potential for a similar hazard of right cardiac thrombosis leading to

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pulmonary embolism (PE) has received little attention. PE and deep vein thrombosis (DVT) are usually viewed as two clinical manifestations of the same disease, venous thromboembolism (VTE). This reflects not only similarities in pathophysiology, but also the fact that the vast majority of PEs stem from an underlying DVT, which may be clinically overt or silent. The PE prevalence in patients with DVT may be as high as 50%,[4–6] the majority of those giving little or no symptoms. In some PE cases, though, no source thrombus can be identified. One explanation may be that such a large part of the deep venous thrombus has been dislodged that the remainder cannot be detected even with sensitive methods, but other sources must be considered.

The occurrence of right intracardiac thrombosis (IT) in patients with PE has indeed been described in several small case series,[7–10] and the prognostic significance of thrombosis associated with right ventricular (RV) dysfunction has been subject to evaluation.[11] The comparative inaccessibility of the right heart to non-invasive diagnostic procedures is the most likely explanation for why no large population studies have yet been conducted to elucidate the prevalence of right atrial (RA) thrombosis and associated absolute PE risks.

For several decades, the city of Malmö in southern Sweden has been a centre for epidemiological research, including clinical and autopsy-based studies of atherosclerotic and other cardiovascular diseases.[12–14] Between 1970 and 1982, close to 24 000 autopsies were performed, prospectively using a standardized protocol and comprising 84% of all in-hospital deaths in the city. The aims of the present study have been to establish the age- and gender-specific prevalence of IT in a population-based autopsy cohort, and to elucidate the relationship between IT and PE.

Methods

Study cohort

Malmö is a city with a single referral centre for post-mortem examinations, the Department of Pathology at Malmö University Hospital. Between 1 January 1970 and 31 December 1982, when the city population declined from 264 000 to 230 000 inhabitants, 35 784 deaths occurred in the Malmö population. According to Swedish legislation at that time, forensic autopsy was mandatory in all deaths occurring outside a hospital. Of 7588 referred cases, forensic autopsy protocols were retrieved in 7569 (99.8%). Among the 28 196 deaths occurring among in-patients at the three hospitals which during this period served the Malmö population, a total of 23 796 clinical autopsies were performed. Hence, the rate of clinical autopsies among in-hospital deaths was 84%, whereas the overall autopsy rate was 88% (31 365/35 784). Owing to differences between clinical and forensic autopsies (the focus of the autopsy, methodology, and variation in time span between death and autopsy), the latter have not been included in this study.

Classification of IT and other pathologies

All autopsies were performed using a standardized protocol and carried out or supervised by senior pathologists. All findings were classified and coded according to the Standardized Nomenclature of Pathology (SNOP), as defined by the College of American Pathologists in 1965. The procedure included examination of the heart cavities and walls. All protocols with one or more of the SNOP codes 32-20-3703, 32-50-3703, 32-30-3703, and 32-60-3703 denoting, respectively, RA thrombosis, RV thrombosis, LA thrombosis, and LV thrombosis, were identified, with or without the presence of SNOP code 32-10-3703, being descriptive of a broad mural adherence of the thrombus. The SNOP codes 32-00-2432 and 32-00-1551 denote, respectively, persistent foramen ovale (PFO) and the presence of intracardiac pacemaker catheter.

In the further analysis of IT, the following patient clusters were identified:

- patients with any IT (thrombus in one or more of the heart cavities);
- patients with right IT (RA and/or RV thrombosis, with or without the presence of LA or LV thrombosis);
- patients with left IT (LA and/or LV thrombosis, with or without the presence of RA or RV thrombosis);
- patients with isolated right IT (RA and/or RV thrombosis only);
- patients with isolated left IT (LA and/or LV thrombosis only);
- patients with both right and left IT (RA and/or RV thrombosis, plus LA and/or LV thrombosis).

Classification of PE

During autopsy, the pulmonary arteries and the lungs were routinely examined for signs of PE, including microscopic examination of lung specimens. All protocols with one or more of the SNOP codes 44-00-3702, 44-00-3710, and 28-00-3710, indicating PE, were identified. PE cases coded with 44-00-3702 and/or 44-00-3710 were further classified as macroscopic PE, whereas cases coded with 28-00-3710 only were classified as microscopic PE.

Classification of causes of death

Death certificates were issued by the pathologist. On the basis of the clinical picture and autopsy findings, an underlying cause of death and up to six contributing causes were determined and classified using the ICD-8 code. In this study, cases coded ICD 410.0–410.9 or 412.0–412.9 were classified as ischaemic heart disease (IHD)-related deaths. Correspondingly, cases coded ICD 140.0–239.9 were classified as cancer-related deaths and cases coded ICD 1.0–139.9 as infection related.

Identification of cases and controls

In a nested case–control study of risk for IT in PE, one PE-free control, matched for gender, age at death, and year

Table 1 Autopsy cohort: patient characteristics, prevalence of IT, and PE

Prevalence of IT	*n* (% of total population)	Female gender *n* (%)	Age at death (years) mean (95% CI)	PFO *n* (%)	Pacemaker catheter *n* (%)	PE prevalence *n* (%)
Any thrombosis						
Yes	1706 (7.2)	862 (50.5)	76.0 (75.5–76.5)	137 (8.0)	63 (3.7)	647 (37.9)
No	22090 (92.8)	10777 (48.8)	72.0 (71.8–72.2)	1356 (6.1)	225 (1.0)	4801 (21.7)
		$P = 0.167$	$P < 0.001$	$P = 0.001$	$P < 0.001$	$P < 0.001$
Thrombus location						
Right atrium[a]	727 (3.1)	380 (52.3)	76.5 (75.8–77.3)	52 (7.2)	30 (4.1)	310 (42.6)
Left atrium[a]	747 (3.1)	409 (54.8)	76.3 (75.6–77.0)	57 (7.6)	24 (3.2)	288 (38.6)
Right ventricle[a]	129 (0.5)	65 (50.4)	73.6 (72.0–75.3)	10 (7.8)	11 (8.5)	71 (55.0)
Left ventricle[a]	542 (2.3)	212 (39.1)	72.7 (71.8–73.6)	48 (8.9)	16 (3.0)	211 (38.9)
Right/left distribution						
Isolated right	515 (2.2)	284 (55.1)	76.9 (76.0–72.2)	34 (6.6)	25 (4.9)	197 (38.3)
Isolated left	895 (3.8)	437 (48.8)	74.8 (74.1–75.5)	77 (8.6)	25 (2.8)	293 (32.7)
Right and left	296 (1.2)	141 (47.6)	75.1 (74.0–76.1)	26 (8.8)	13 (4.4)	157 (53.0)
No thrombosis	22090 (92.8)	10777 (48.8)	72.0 (71.8–72.2)	1356 (6.1)	225 (1.0)	4801 (21.7)
		$P = 0.039$	$P < 0.001$	$P = 0.007$	$P < 0.001$	$P < 0.001$

[a]Groups not mutually exclusive.

of death, but otherwise randomly chosen, was assigned to each PE case. Similarly, in another nested case–control study of PE risk in IT, four IT-free controls were assigned to each case of IT.

Statistical methods

Distributions were expressed in terms of means and variance. One-way analysis of variance (ANOVA) was used to evaluate differences in mean and χ^2 test to evaluate differences in proportions, adopting two-sided significance tests.

The robustness of the association between IT and PE was explored by sensitivity analysis of subgroups according to causes of death. These analyses were performed without adjustments for multiplicity of significance level. In addition, logistic regression analyses were performed to investigate the partial effects on PE risk of right and left IT, when entering gender, age, and death cause from the univariate analyses.

The analysis of the nested case–control study of PE, one-to-one matched, was performed using a stratified analysis in which the strata consisted of the collection of matched pairs. The Mantel–Haenszel χ^2 test for association based on 5448 strata was performed and the Mantel–Haenszel odds ratio was calculated as a summary odds ratio that adjusts for the matched variables.

Similarly, the nested case–control study of IT, four-to-one matched, was also analysed using the Mantel–Haenszel stratification method. In this case, the strata consisted of the collection of matched sets including five subjects each, and the calculations were thus based on 1706 strata.

Results

Prevalence of IT at autopsy

Among the 23 796 autopsies, IT was found in 1706 patients (7.2%) (*Table 1*). The distribution of intracardiac thrombi is depicted in *Figure 1*. Mean age at death was 76 years (*Table 1*) (*Figure 2*). LV thrombosis was more commonly found in men ($P < 0.001$), with lower mean age at death in comparison with RV thrombosis. The prevalence of RA and LA thrombosis was similar, and RA thrombosis was seven times as frequent as RV thrombosis.

Patients who had died from IHD had 3.2 times higher odds for right-sided thrombosis (95% CI: 2.7–3.6) and 4.7 times higher odds for left-sided IT (95% CI: 4.2–5.3) in comparison with non-IHD deaths (*Table 2*). Cancer-related deaths and infection-related deaths were, on the other hand, associated with an underrisk of IT.

A PFO was found in 8.0% (137/1706) of the patients with IT, compared with 6.1% (1356/22 090) of all thrombus-free patients ($P = 0.001$). Although there was an association between the presence of pacemaker catheters and IT, the vast majority (96.3%) of thrombosis patients had no pacemaker (*Table 1*).

PE risk in patients with IT

Thirty-eight per cent (647/1706) of the patients where an IT was found at autopsy also had a manifest PE (*Table 1*). *Figure 1* illustrates the relationship between the anatomical localization of IT and PE prevalence. Fifty-five per cent of patients with RV thrombosis and 53% of patients with both right and left IT also had PE (*Table 1*).

No association between PFO and PE was found in patients with IT: the prevalence of PE was 35.8%

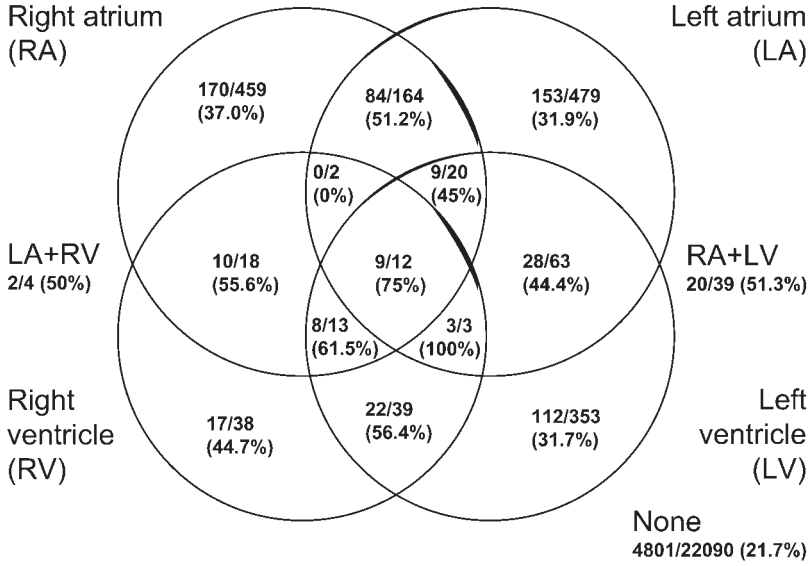

Figure 1 Distribution of IT in 23 796 consecutive autopsies between 1970 and 1982. Figures denote number of PEs/number of patients with intracardiac thrombus in respective locations (percentage of patients with PE).

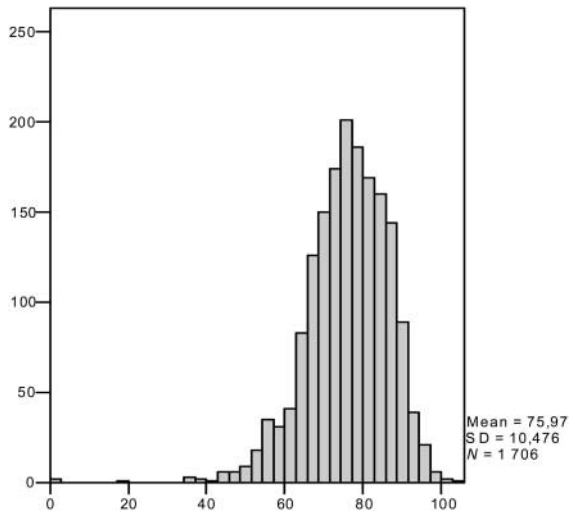

Figure 2 Distribution of age at death in cases with IT found at autopsy.

(49/137) in those with PFO and 38.1% (598/1569) in those without PFO ($P = 0.646$). Similarly, no significant differences in PE rate were found between thrombosis patients with (27.0%; 17/63) or without (38.3%; 630/1643) a pacemaker catheter ($P = 0.085$).

The association between PE and right vs. left IT remained when stratifying for death from IHD and for death from cancer disease, respectively (*Table 2*). Of patients dying from infectious disease, right-sided thrombosis occurred only in 11 (2%), but seven of those (64%) had developed PE, in contrast to 21% in the control group (OR 6.5; 95% CI 2.3–23). When controlling for these death causes and for gender and age at death in a logistic regression analysis, right and left IT were still, independently of each other, associated with an OR (95% CI) of 2.3 (2.0–2.7) and 2.0 (1.8–2.2), respectively (*Table 2*).

Age- and gender-adjusted risk for PE in IT

In a nested case–control study, cases with IT had twice as high odds for PE as controls, matched for gender, age, and year of death (95% CI 1.8–2.2) ($P < 0.001$) (*Table 3*). Correspondingly, the association with isolated left IT was less pronounced (OR 1.6; 95% CI 1.4–1.9) ($P < 0.001$), whereas the odds for PE was 3.4 times higher in cases with combined right and left IT than in controls (95% CI 2.6–4.4) ($P < 0.001$).

IT in patients with PE: prevalence and risk

PE was present at autopsy in 22.8% (5448/23 796) of all patients. Of these, 804 (14.8%) had microscopic PE. IT was found in 647 (11.9%) of all PE cases, compared with 342 (6.3%) of the controls, matched for gender, age at death, and year of death, corresponding to an OR (95% CI) of 2.0 (1.8–2.3) ($P < 0.001$) (*Table 4*). Right-sided IT was 2.4 times more common among PE cases (95% CI: 2.0–2.9) ($P < 0.001$) than among controls, whereas the odds for combined right and left IT was three times higher among cases than among controls (95% CI: 2.2–4.1) ($P < 0.001$).

In 62.1% (220/354) of the cases with PE in the presence of right IT, no other potential source of embolization could be identified at the autopsy examination of the caval-, iliac-, and femoral veins. Thus, right IT was the only identified source of emboli in 4.0% (220/5448) of all patients with PE in the autopsy cohort.

Table 2 Prevalence of right and left IT in relation to IHD-related, cancer-related, and infection-related causes of death and associated risk of PE, when stratifying for cause of death, and in multivariate analysis

Cause of death	*n*	Right IT		PE in relation to right IT			Left IT		PE in relation to left IT		
		n (%)	OR (95% CI)	Right IT	PE (%)	OR (95% CI)	*n* (%)	OR (95% CI)	Left IT	PE (%)	OR (95% CI)
All patients				Yes	354 (44)	2.7 (2.4–3.1)			Yes	450 (38)	21 (1.9–2.4)
				No	5094 (22)	1[a]			No	4998 (22)	1[a]
IHD related											
Yes	7456	470 (6.3)	3.2 (2.7–3.6)	Yes	200 (43)	3.0 (2.5–3.6)	791 (10.6)	4.7 (4.2–5.3)	Yes	293 (37)	2.5 (2.1–2.9)
				No	1382 (20)	1[a]			No	1289 (19)	1[a]
No	16340	341 (2.1)	1[a]	Yes	154 (45)	2.7 (2.2–3.4)	400 (2.4)	1[a]	Yes	157 (39)	2.1 (1.7–2.6)
				No	3712 (23)	1[a]			No	3709 (23)	1[a]
Cancer related											
Yes	8512	118 (1.4)	0.3 (0.2–0.4)	Yes	49 (42)	2.2 (1.5–3.2)	156 (1.8)	0.3 (0.2–0.3)	Yes	57 (37)	1.8 (1.3–2.5)
				No	2043 (24)	1[a]			No	2035 (24)	1[a]
No	15284	693 (4.5)	1[a]	Yes	305 (44)	3.0 (2.5–3.5)	1035 (6.8)	1[a]	Yes	393 (38)	2.3 (2.0–2.7)
				No	3051 (21)	1[a]			No	2963 (21)	1[a]
Infection related											
Yes	589	11 (1.9)	0.5 (0.3–0.9)	Yes	7 (64)	6.5 (2.3–23)	15 (2.5)	0.5 (0.3–0.8)	Yes	7 (47)	3.2 (1.2–9.1)
				No	45 (21)	1[a]			No	122 (21)	1[a]
No	23207	800 (3.4)	1[a]	Yes	347 (43)	2.7 (2.3–3.1)	1176 (5.1)	1[a]	Yes	443 (38)	2.1 (1.9–2.4)
				No	4972 (22)	1[a]			No	4876 (22)	1[a]
LR[b]						2.3 (2.0–2.7)					2.0 (1.8–2.2)

[a]Reference category.
[b]Logistic regression of PE risk when entering as covariates: right IT, left IT, gender, age at death and IHD, cancer, and infection as cause of death.

Table 3 PE in cases with IT and in controls, matched for gender, age at death, and year of death: prevalence and OR

Patient category	PE prevalence						
	No PE *n* (%)	Any PE			Macroscopic PE		
		n (%)	*P*-value[a]	OR (95% CI)[a]	*n* (%)	*P*-value[a]	OR (95% CI)[a]
Any IT							
Cases	1059 (62.1)	647 (37.9)	<0.001	2.0 (1.8–2.2)	549 (34.1)	<0.001	1.9 (1.7–2.2)
Controls	5204 (76.3)	1620 (23.7)		1[b]	1396 (21.2)		1[b]
Isolated right IT							
Cases	318 (61.7)	197 (38.3)	<0.001	2.0 (1.6–2.4)	176 (35.6)	<0.001	2.0 (1.6–2.5)
Controls	1570 (76.2)	490 (23.8)		1[b]	429 (21.5)		1[b]
Isolated left IT							
Cases	602 (67.3)	293 (32.7)	<0.001	1.6 (1.4–1.9)	240 (28.5)	<0.001	1.5 (1.3–1.8)
Controls	2744 (76.6)	836 (23.4)		1[b]	725 (20.9)		1[b]
Both right and left IT							
Cases	139 (47.0)	157 (53.0)	<0.001	3.4 (2.6–4.4)	133 (48.9)	<0.001	3.5 (2.7–4.7)
Controls	890 (75.2)	294 (24.8)		1[b]	242 (21.4)		1[b]

[a]In comparison with no PE.
[b]Reference category.

Table 4 IT in cases with PE and in controls, matched for gender, age at death, and year of death: prevalence and OR

Occurrence of IT		PE cases $n = 5448$ (%)	Controls		
			$n = 5448$ (%)	*P*-value	OR (95% CI)
Any IT	Yes vs. no	647 (11.9)	342 (6.3)	<0.001	2.0 (1.8–2.3)
Right IT	Yes vs. no	354 (6.5)	155 (2.8)	<0.001	2.4 (2.0–2.9)
Left IT	Yes vs. no	450 (8.3)	242 (4.4)	<0.001	1.9 (1.6–2.3)
Isolated right IT	Yes vs. no IT	197 (3.9)	100 (1.9)	<0.001	2.1 (1.6–2.7)
Isolated left IT	Yes vs. no IT	293 (5.8)	187 (3.5)	<0.001	1.7 (1.4–2.0)
Both right and left IT	Yes vs. no IT	157 (3.2)	55 (1.1)	<0.001	3.0 (2.2–4.1)

Discussion

The possibility to detect LA thrombosis with ultrasonography and the outcome of large-scale intervention trials have led to an increased awareness of the associated risk of embolic stroke.[1–3,15] Guidelines have been issued and implemented.[16,17] In view of the symmetry of the heart, it is quite conceivable that right cardiac thrombosis might have a similar role for the development of PE. IT has indeed been described from PE case series,[4–11] but in the absence of population-based studies, the true prevalence is obscure. The lack of knowledge possibly reflects the comparable inaccessibility of the right atrium for non-invasive evaluation and the difficulties of correctly assessing PE. In this autopsy study representing 84% of all in-hospital deaths during a 13-year period, IT was present in 7% of all cases. Right-sided thrombosis was as common as left-sided thrombosis. Depending on the distribution of thrombosis, between one-third and half of these patients also had a PE.

What then does IT represent? Among conditions associated with LA thrombosis, atrial fibrillation predominates.[15,18] Although the present study does not allow an assessment of this or other functional diagnoses, the high concordance between right- and left-sided thrombosis and the advanced age of these patients are indirect indicators. Among other causes, IT may be formed at the scar after a myocardial infarction, and an association was also found in the present study. Tumour emboli caught in transit and thrombosis secondary to infectious lesions are infrequent explanations but should be considered in an autopsy cohort of this magnitude. Right cardiac thrombosis was present in only 2% of patients dying from infectious disease, but was associated with a 6.5-fold increased prevalence of PE. As with any sensitivity analysis of subgroups, some caution is warranted when interpreting multiple analyses.

Some aspects should be addressed when attempting to generalize from these results. Being an autopsy study, it represents a selection of the sickest patients. Fresh clots resulting from terminally hypodynamic circulation were not counted, but it cannot be ruled out that in some patients, IT might reflect a pre-terminal state. This would result in an overestimation of prevalence, but probably not cause bias or affect the PE risk in those patients who had a right IT. Population data with which to compare our results are scarce, but in a unique transoesophageal echocardiogram (TOE) study of

a representative sample of the general population of healthy elderly, Roijer *et al.*[19] found a potential cardioembolic source in the left atrium in as many as 38% of all subjects.

Would the study, if performed today, have yielded similar results? Here one must consider the implementation of antithrombotic treatment in atrial fibrillation[16,17] and the increased use of low-dose aspirin. Given the high age and the comorbidity pattern in most patients of the present study, the imputed effect of aspirin in this context can be questioned.[16,17] Diligent use of anticoagulants will probably lower the prevalence of IT, but not eradicate it—in the large TOE study performed by Agmon *et al.*,[15] half of the patients with a finding of atrial thrombosis were on anticoagulant treatment. Moreover, even in recent studies, far from all eligible atrial fibrillation patients as yet receive effective anticoagulation.[20,21]

More relevant than the magnitude of prevalence of right cardiac thrombosis is the question of associated PE risk, and especially, to what extent this represents causality. A cross-sectional study has limitations over a longitudinal one for inference on causality, and here, prospective clinical studies are needed. Assessment of strength of association is another tool for inference on causality in epidemiological studies.[22] An increased PE risk in patients with solitary left thrombosis can only be explained, in the absence of PFO, by a state of hypercoagulability, and in these patients a moderate 50% increased risk was found. In comparison, in patients with isolated right thrombus, which then might be causative for PE, the overrisk was 100%, and in patients with bilateral thrombosis, an excess PE risk of 250% was found.

We conclude from this population-based autopsy study that right IT, though difficult to assess in clinical practice, is as common as left IT. Of patients dying from or with PE, 7% had right IT as a potential cause, which constituted the only evident source for embolism in 4% of all cases. The diagnosis should be considered in all cases of PE, especially in patients with atrial fibrillation or myocardial infarction and in the absence of confirmed DVT.

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