Published Ahead of Print on July 16, 2012, as doi:10.3324/haematol.2012.069195.

haematologica
the hematology journal

Early Release Paper

Finding the origin of pulmonary embolism with a total-body magnetic resonance direct thrombus imaging technique

by Kirsten van Langevelde, Alexandr Sramek, Patrice W.J. Vincken, Jan-Kees van Rooden, Frits R. Rosendaal, and Suzanne C. Cannegieter

Haematologica 2012 [Epub ahead of print]

Citation: van Langevelde K, Sramek A, Vincken PW, van Rooden JK, Rosendaal FR, and Cannegieter SC. Finding the origin of pulmonary embolism with a total-body magnetic resonance direct thrombus imaging technique. Haematologica. 2012; 97:xxx doi:10.3324/haematol.2012.069195

Haematologica (pISSN: 0390-6078, eISSN: 1592-8721, NLM ID: 0417435, www.haematologica.org) publishes peer-reviewed papers across all areas of experimental and clinical hematology. The journal is owned by the Ferrata Storti Foundation, a non-profit organization, and serves the scientific community with strict adherence to the principles of open access publishing (www.doaj.org). In addition, the journal makes every paper published immediately available in PubMed Central (PMC), the US National Institutes of Health (NIH) free digital archive of biomedical and life sciences journal literature.

DOI: 10.3324/haematol.2012.069195

Finding the origin of pulmonary embolism with a total-body magnetic resonance direct thrombus imaging technique

Running title: Finding the irigin of pulmonary embolism

Kirsten van Langevelde,[1] Alexandr Sramek,[2] Patrice W.J. Vincken,[3] Jan-Kees van Rooden,[4] Frits R. Rosendaal,[1,5] and Suzanne C. Cannegieter[1]

[1]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands; [2]Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands; [3]Department of Radiology, Rijnland hospital, Leiderdorp, the Netherlands; [4]Department of Radiology, Haga Teaching Hospital, The Hague, the Netherlands, and [5]Department of Thrombosis and Haemostasis, Leiden University Medical Center, Leiden, the Netherlands

Correspondence

Suzanne C. Cannegieter, Department of Clinical Epidemiology C7-P, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Phone: international +31715264037. Fax: international +31715266994. E-mail: S.C.Cannegieter@lumc.nl

DOI: 10.3324/haematol.2012.069195

Abstract

Background

Pulmonary embolism is considered to originate from embolization of a deep-vein thrombosis, resulting in two manifestations of one disease: venous thrombosis. However, in up to 50% of patients with pulmonary embolism no deep-vein thrombosis is found with ultrasonography. An explanation for this low proportion is currently lacking. Other imaging modalities may increase deep-vein thrombosis yield in the calf or in the abdominal region. Alternatively, not all pulmonary emboli may originate from deep-vein thrombosis in the extremities. We searched for the origin of pulmonary embolism, by performing total-body Magnetic Resonance Imaging-scans to visualize thrombi.

Design and Methods

99 patients with a Computed Tomography confirmed first pulmonary embolism underwent a Magnetic Resonance Direct Thrombus Imaging-scan, a validated technique using endogenous contrast. Additionally, acquired and genetic risk factors were assessed.

Results

No thrombus was found in 55 patients, leaving 44 patients with thrombus. The commonest origin was the lower leg; 12 patients had isolated calf vein thrombosis, 5 had isolated superficial vein thrombosis.

Conclusions

In less than half of patients with pulmonary embolism a peripheral thrombus was found with Magnetic Resonance Imaging. We proposed several hypotheses to explain the absence of thrombi, such as cardiac thrombus origin or embolization of the complete deep-vein thrombosis. The possibility that pulmonary embolism arises de novo in the lungs, due to local inflammation driven coagulation, needs to be considered.

DOI: 10.3324/haematol.2012.069195

Introduction

Since autopsy studies by Virchow in the mid 1800s, pulmonary embolism (PE) is thought to originate from embolization of a deep-vein thrombosis (DVT), resulting in two clinical manifestations of one disease: venous thrombosis (VT). However, in up to 50% of patients with PE no DVT is found with ultrasonography or contrast venography studies.[1-6] A suitable explanation for this low proportion is currently lacking.

Compression ultrasonography (CUS) is presently the leading diagnostic modality for the diagnosis of DVT, with a sensitivity of 96% and specificity of 98% for symptomatic proximal DVT.[7] A disadvantage of CUS is its reduced accuracy when it comes to below knee thrombi or pelvic thrombi. Thrombi in the calf veins extend to proximal veins in 20-30% of cases, and may embolize from the calves or after extension, contributing to PE occurrence.[8] Calf veins and pelvic veins may be an overlooked source of PE that could explain the 20-50% of thrombi missed by CUS imaging. Therefore, other imaging modalities may lead to a larger yield of DVTs, both in the abdominal and pelvic region as in the calf veins. Combined CT pulmonary angiography (CTPA) and CT venography has been performed to search for abdominal thrombi. By extending the scan from the lungs to the pelvis and legs, Nchimi et al. found 10% of DVTs above the inguinal ligament.[9]

A validated, new and highly sensitive technique in diagnosing DVT is magnetic resonance direct thrombus imaging (MRDTI).[10,11] This is a non-invasive technique without the need of gadolinium contrast. Unlike most imaging techniques, which show the thrombus as a filling defect, MRDTI shows the thrombus itself and suppresses background signal. This method is based on the transformation of haemoglobin into methemoglobin when a thrombus is formed. Using a T1 sequence, methemoglobin in the thrombus gives a high signal that disappears after about 6 months. A sensitivity of 98% and a specificity of 96% were found for MRDTI compared with ultrasound or venography in 101 patients with symptomatic DVT.[10] Since physical accessibility of veins plays no role in MRI, this method allows visualization of thrombi at all anatomical loci.

DOI: 10.3324/haematol.2012.069195

Similar to the question about the anatomical origin of a PE, risk factors for migration of a DVT towards the lungs are not well known and are clearly not uniform. The most prominent differential risk factor that has been found is the factor V Leiden mutation, which causes APC resistance and thereby increases thrombotic risk. Factor V Leiden increases the incidence of DVT (odds ratios ranging from 3 to 10)[1,12-15] more than that of PE (odds ratios ranging from 1 to 5),[16-18] compared with non-carriers. This differential effect of factor V Leiden has become known as the factor V Leiden paradox, and has not been found for other genetic risk factors for VT.[19,20] Some acquired factors also differently affect the risk of DVT and PE, e.g., use of oral contraceptives is associated with a 4-fold increased risk of PE and an almost 7-fold increased risk of DVT,[19,21] while COPD, asthma and pneumonia mainly increase the risk of PE.[22-24] Therefore, considering DVT and PE as simply manifestations of one disease ("venous thromboembolism") appears not justified.

We set up the PEDLAR (Pulmonary Embolism: Development, Localization, And Risk factors) study to determine where PE originated from, and to assess whether all PEs were accompanied by a DVT. When a DVT was present, we described anatomical location and the number of affected veins. To this effect, we performed total-body MRI scans to visualize thrombi from calf veins up to subclavian veins. In addition, we studied to what extent risk factors for an isolated PE differ from risk factors for a PE with concomitant DVT.

Design and Methods

Patient enrollment in the PEDLAR study started in November 2008 and closed in February 2011. All patients above 18 years with a first PE confirmed by CTPA, from the Leiden University Medical Center (Leiden, the Netherlands) and the Rijnland hospital (Leiderdorp, the Netherlands) were invited to undergo a total-body MRDTI scan within seven days after diagnosis. Inclusion into the study in the Rijnland hospital started one year later, in October 2009. Approval for this study was obtained from the Medical Ethics Committees of both centers. All participants provided written informed consent according to the Helsinki

declaration. Patients with a PE were selected at the Radiology departments of the two medical centers. The study comprised a single visit of one hour to the LUMC where all tests took place.

The presence of a pacemaker was an exclusion criterion for the study. In addition, claustrophobia and high body weight were contraindications to undergo MRI scanning. No strict cut-off for body weight was applied, as the distribution of body weight was more important than weight itself to fit into the scanner.

A questionnaire on risk factors for VT was filled in by all patients. The questionnaire contained questions on family history of VT, recent travel, surgery, cancer, and use of the contraceptive pill. As atrial fibrillation may give rise to thrombus formation in the right heart, and could thereby be a possible source of PE, electrocardiograms (ECGs) were reviewed as well as the medical charts. Patients were categorized as “atrial fibrillation positive” when they had a documented history of atrial fibrillation, or when the ECG made at the time of PE diagnosis showed atrial fibrillation, and negative when otherwise. Blood was drawn for analysis of the factor V Leiden and prothrombin G20210A mutation. These were determined by polymerase chain reactions using the TaqMan assay. A detailed description of these methods has been published previously.[25] In case blood draws were not possible, DNA was collected via a buccal swab.

The total-body scan was performed on a Philips 1.5 Tesla MRI scanner (Philips Medical Systems, Best, The Netherlands), with extended table construction. The MRDTI protocol consisted of a T1-weighted, 3D gradient-echo sequence developed by Moody and colleagues and modified to Philips equipment by Westerbeek et al.[11,26] The MRI protocol has been described more extensively in a review on MR imaging of venous thrombosis.[27] Pulmonary structures (including the pulmonary arteries) could not be imaged with the MRDTI scan we used, due to the free-breathing scanning protocol. Therefore, we did not attempt to confirm the PEs detected by CTPA by MRI.

We aimed to enroll 100 patients with a first PE in this observational study. We assessed the anatomic location of DVTs, the number of affected veins per patient, and whether the affected veins were proximal or distal. Calf vein

DOI: 10.3324/haematol.2012.069195

thrombosis was included in the analysis, and superficial vein thrombosis was documented separately from DVT. Superficial vein thrombosis was often seen in a tortuous varicose vein, thrombus length was therefore not measurable. To achieve a clear overall interpretation of the localization of thrombi on MRI, we subdivided the relevant veins into seven exclusive sections. The sections were independent of the side of thrombosis. The first section was abdominal, including the inferior caval vein and the pelvic veins or any other abdominal veins. The second section was the upper leg, including the common femoral vein, the superficial femoral vein, the profunda femoris vein, and the popliteal vein. The third section was formed by the calf veins and, as mentioned previously, deep and superficial veins were assessed separately. Occlusion of these three sections could be present in isolation or in combinations, i.e.: a combination of the abdominal section and the upper leg, the abdominal veins and the calf veins, all leg veins (upper and lower leg), and finally the abdominal, upper and lower leg veins together. The MR images were scored by consensus of two radiologists (AŠ and CJvR) who both had more than three years of experience with Magnetic Resonance Angiography. During the scoring process both radiologists were blinded for the DVT status on CUS. The prevalence of acquired and genetic risk factors in PE patients with and without concomitant DVT was calculated in percentages, with a corresponding 95% confidence interval (CI).

Results

From October 2008 to February 2011 we enrolled 102 PE patients into the study. Figure 1 shows the flowchart of the study by medical center. The majority of participants (80, 78%) came from the Leiden University Medical Center, whereas 22 (22%) came from the Rijnland hospital. Participation in the Leiden University Medical Center was 40% and in the Rijnland hospital 31%. All MRI scans took place at the Leiden University Medical Center. Of 102 patients who were enrolled, 99 successfully completed the MRI. Three MRIs were not completed due to claustrophobia, a waist circumference too large to fit in the MRI, and a technical problem. Patient characteristics are shown in Table 1. Median age of

DOI: 10.3324/haematol.2012.069195

the patients was 54 (range 18-84) years. There were more male than female participants in the study, 61% versus 39%, respectively. Of the study participants, 13 had undergone an ultrasound examination of the legs on clinical request. Of these, 10 patients were found to have concomitant DVT.

Table 2 shows the localization of thrombi in all PE patients. No thrombus was found in 55 (56%) patients, leaving 44 (44%) patients in whom a thrombus was found. We found no thrombi in the arms or upper extremity veins. The sides of the body where thrombi were found on MRI were not equally distributed: the majority was present in the left extremity (61%), 30% was right-sided, and 9% was bilateral. Most patients with a thrombus had 2 or more veins affected (25 out of 44, 57%). 19 out of 44 patients (43%) had only one vein that was occluded. The predefined venous segments of the anatomical localization of thrombi are shown in Figure 2 (independent of the side of DVT). We found 16 (36%) patients with a thrombosis on MRI to have an occlusion in both the upper and lower leg. The most common origin was the lower leg; here 12 patients (27%) had isolated deep calf vein thrombosis, and 5 (11%) presented with isolated superficial vein thrombosis confined to the calf. Abdominal thrombi were rare (3 patients, 7%).

We assessed common acquired and genetic risk factors in all participants (Table 3). Overall, 21% of patients were aged over 65 years. One in four patients had an active malignancy at the time of PE diagnosis. A similar percentage was found for recent surgery. These risk factors were equally present in PE patients with and without a DVT on MRI. Minor leg injuries were present more often in patients with DVT than in those without DVT, in 11% and 5% respectively. One or more immobilization risk factors (i.e., bedrest of more than four days in the past eight weeks, air travel of more than eight hours, travel by car or train longer than four hours) were present in 27% of patients with DVT, and in 41% of patients without DVT. As for the two genetic risk factors that were measured in this study, we found a higher prevalence of factor V Leiden in patients with DVT on MRI (14%) than in those without DVT (7%). For the prothrombin (G20210A) mutation, prevalences did not differ much, i.e., 4% in PEs without DVT and 2% in PEs with DVT.

DOI: 10.3324/haematol.2012.069195

Discussion

We performed a total-body MRI scan in 99 patients with PE, and could not detect a peripheral thrombus in more than half of the patients. We had expected to detect thrombi in the majority of cases, and a substantial number in the abdominal or pelvic region where CUS cannot readily detect thrombi. In the following section we present different potential explanations for these surprising findings, some of which we can reject.

Explanation 1: the MRDTI technique is not sensitive enough to detect all DVTs

Two earlier studies have shown that sensitivity and specificity of the MRDTI technique are superb for acute DVT of the leg, between 95-98% and 96-100%, respectively.[11,28] The first study compared MRDTI with a reference standard of venography and CUS or venography alone;[28] the second study used CUS as gold standard for imaging of DVT.[11] Our study was not performed to calculate sensitivity and specificity estimates of the MRDTI scanning technique. Therefore we did not perform ultrasound examinations on all patients by protocol. However, in those patients who underwent CUS as a part of clinical diagnostic work-up, we found that of 13 patients, 10 had a DVT. The MRI showed a DVT in 9 out of these 10 patients (i.e., a sensitivity of 90%). The DVT that was missed was a (deep) calf vein thrombosis of the left leg. Therefore, even when we assume that not all DVTs were detected by MRDTI scanning, this explanation may account for some, but is unlikely to account for 56% of missing thrombi.

Explanation 2: PEs without a DVT on MRI are due to “therapeutic embolization”

This explanation comprises that in patients with PE without DVT on MRI, a DVT had been present but was completely dislodged to the pulmonary arteries at the time of scanning. Yet, this theory seems unlikely as an explanation for all of the

missing DVTs, as is supported by data from postmortem studies. These studies showed that only part of the clot (usually the free-floating tail) breaks off and embolizes.[29-31] Furthermore, one would expect that more time between diagnosis of PE and MRI scanning would be related to a lower chance of finding a thrombus. We performed a logistic regression analysis to address this question, using the presence or absence of DVT as an outcome and the number of days between PE diagnosis and MRI scan as a continuous covariable. Our data showed no association between identification of a DVT and the number of days between diagnosis and MRI, with an OR of 0.99 (95% CI 0.81-1.21).

Explanation 3: PE has a cardiac origin

Case reports describing PE due to right atrial thrombi in atrial fibrillation have led us to consider this as an alternative origin of PE.[32,33] In a recent case-control study based on ICD discharge codes in the Danish National Patient Registry, heart disease was shown to be a risk factor for PE without concomitant DVT, with an over 40-fold increased risk for the first three months after myocardial infarction or heart failure.[34] For DVT with or without PE, this risk was 10- to 20-fold increased. The risk was more pronounced for right-sided heart disease, suggesting a direct relation with the thrombus in the pulmonary arteries. Two previous studies also showed that patients with atrial fibrillation, mitral valve stenosis or dilated cardiomyopathy are at increased risk to develop isolated PE. The authors concluded that heart diseases could be a source of PE, due to the development of right-sided cardiac thrombi.[35,36] In our study, in the group of PE patients without DVT on MRI, there were no patients with documented heart failure. Two out of 55 patients had atrial fibrillation (4%). The absence of heart failure and the low proportion of atrial fibrillation make it unlikely that cardiac thrombi would explain the absence of DVTs in over half of the PE patients.

Explanation 4: PE originates from local thrombus formation in the lungs

From an alternative etiological point of view, PE may be a local phenomenon, starting in the pulmonary arteries. Previously, the hypothesis has been proposed of central PE being caused by DVT and peripheral, smaller PE being caused by local inflammatory reactions in the pulmonary arteries.[31] The idea of PE due to local inflammatory processes was described in two studies performed in trauma patients.[31,37] Autonomic dysfunction is one of the consequences of trauma, which may lead to adrenergia and inflammation that together promote coagulation. Hypoxia may also activate the endothelium.[31,37] Yun et al. conclude that embolic disorders such as PE may represent asynchronous systemic phenomena rather than a clot migration process, when adrenergia and inflammation are present.[38] In addition, COPD and asthma may cause local clots, as persistent low-level systemic inflammation is present in these patients.[22,24] Data from a nested case-control study showed a 3.6-fold increased risk of PE for patients with mild COPD, and a 7.5-fold increased risk of PE for severe COPD. No increased risk was found for DVT.[22] We recently found that pneumonia increased the risk of PE in the MEGA study, with an OR of 8.1 (95% CI 6.2-10.6). For DVT alone, the OR was 3.0 (95% CI 2.2-4.0).[23] Inflammation affects coagulation via different mechanisms: via tissue factor mediated thrombin generation, and via the impairment of anticoagulant pathways, the protein C system in particular.[39] In asthma patients impaired fibrinolysis has been described. Protease-activated receptors have been pointed out as the molecular link between coagulation and allergic inflammation in asthma.[24] In addition, coagulation can be further enhanced by the complement system that is activated during inflammation. One might speculate on local inflammation of the vessel wall leading to thrombus formation.

Another argument that supports the possibility of local PE is that of recurrent events. If DVT and PE are manifestations of the same disease, the anatomical location of recurrence would be expected to be independent of the location of the first event. However, PE patients are more likely to develop another PE when a recurrence occurs, while patients with DVT recur as a DVT more often than expected.[40] In addition, patients with isolated PE are less likely

to experience a recurrent event than DVT patients, confirming that isolated PE may be a different entity.[41]

In this study, calf veins were frequently affected in patients with PE (12 patients with thrombi in deep veins and 5 with thrombi in superficial calf veins). Although similar findings have been published previously,[5,42-44] others have stated that as a starting point of PE, distal thrombi are not relevant.[45,46] Of note, from our data we can not determine whether in patients with calf vein DVT a more proximal part had also been present and embolized to the lungs, nor can we estimate the risk of embolization of calf vein thromboses. We found thrombi present only in the abdominal vein segment in 3 out of 44 patients (7%).

We compared our findings to other studies that assessed thrombi above the level of the inguinal ligament, where imaging of DVT was performed either with CT venography or with MRA and found inconsistent results. Nchimi and colleagues imaged PE by CTPA followed several minutes later by CT venography for assessment of DVT. The study population had a mean age of 61 years (range 19-100 years). Out of 272 PE patients, 200 were found to have concomitant DVT (74%). Thrombi above the level of the inguinal ligament were found in 10% of patients with PE, similar to our findings.[9] In addition, isolated below-knee thrombi were found in more than half of PE patients, and the authors conclude that CT venography has to be performed including the calves down to the level of the ankle. Velmahos et al. performed combined CTPA and CT venography in 46 trauma patients with PE. Mean age was 56 years. Only 7 out of 46 (15%) of patients had a concomitant DVT, of which 1 was in the abdominal segment.[31]

Stern et al. assessed DVT using MRA in 24 PE patients with negative CUS findings (mean age 49, range 18-83). Of these patients 7 were found to have pelvic DVT (29%) and 17 had no concomitant DVT. However, these results are not comparable to our study methods, as we did not select patients with a negative CUS, but only with a CTPA proven PE.[47]

DOI: 10.3324/haematol.2012.069195

Of the risk factors we analyzed, the most noticeable finding was that the factor V Leiden mutation was present more often (14%) in PE patients with a concomitant DVT, than in patients with PE alone (7%). This confirms previous findings, which showed that patients with both PE and DVT resemble the DVT patients more than the isolated PE patients concerning factor V Leiden prevalence.[13] As for minor leg injuries, it seems plausible that patients with an injury of the leg are likely to develop a DVT locally, part of which could embolize later.[19] Isolated PE patients indeed had a lower prevalence (5%) of minor leg injuries than patients with a concomitant DVT (11%). A limitation to this study is numbers were small for assessment of differences in risk factors between patients with and without a DVT. Therefore the results that we found have to be interpreted carefully and need to be replicated in larger studies.

In summary, in this etiological study we aimed to locate the origin of PE and thereby increase the yield of DVTs that were otherwise missed on CUS examinations. We found DVT in less than half of all PE patients using a total-body MRI technique, and proposed several hypotheses to explain the absence of DVTs in the majority of patients. Limited sensitivity of MRDTI, complete embolization of the DVT, or a cardiac clot origin could not sufficiently explain the absence of thrombi. We postulate therefore that in some cases PE may arise de novo in the lungs, which could be a new explanation for the origin of PE without concomitant DVT.

DOI: 10.3324/haematol.2012.069195

Acknowledgements

We acknowledge all patients who participated in the study.

We thank the clinicians from the Rijnland and LUMC hospital for their cooperation with recruitment of patients into the study.

We thank Guido R. van Haren for technical support with the MRI scanning protocol.

We thank Petra J. Noordijk for performing the laboratory measurements for the DNA analyses.

We thank Hans A. Vogelaar for developing a PROMISE web database for the study.

We thank Anne Bosch for administrative support with the enrollment of patients.

Funding Source

This study was supported by Netherlands Heart Foundation grant number 2009B050. The funding organisation is a public institution and had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Authorships and disclosures

S.C.C.: Design of the analyses, revision of the manuscript.

F.R.R.: Study concept and design, revision of the manuscript.

A.S.: Study concept and design, reading of MRI-scans, revision of the manuscript.

P.W.J.V.: Study coordinator Rijnland Hospital, revision of the manuscript.

J.C.v.R.: Reading of MRI-scans, revision of the manuscript.

K.v.L.: Study coordinator LUMC, drafting of the manuscript, statistical analyses.

Disclosure of Conflicts of Interest

None

DOI: 10.3324/haematol.2012.069195

References

1. Martinelli I, Cattaneo M, Panzeri D, Mannucci PM. Low prevalence of factor V:Q506 in 41 patients with isolated pulmonary embolism. Thromb Haemost. 1997;77(3):440-3.

2. Yamaki T, Nozaki M, Sakurai H, Takeuchi M, Soejima K, Kono T. Presence of lower limb deep vein thrombosis and prognosis in patients with symptomatic pulmonary embolism: preliminary report. Eur J Vasc Endovasc Surg. 2009;37(2):225-31.

3. Jimenez D, Aujesky D, Diaz G, Monreal M, Otero R, Marti D, et al. Prognostic significance of deep vein thrombosis in patients presenting with acute symptomatic pulmonary embolism. Am J Respir Crit Care Med. 2010;181(9):983-91.

4. Girard P, Sanchez O, Leroyer C, Musset D, Meyer G, Stern JB, et al. Deep venous thrombosis in patients with acute pulmonary embolism: prevalence, risk factors, and clinical significance. Chest. 2005;128(3):1593-600.

5. Kruit WH, de Boer AC, Sing AK, van Roon F. The significance of venography in the management of patients with clinically suspected pulmonary embolism. J Intern Med. 1991;230(4):333-9.

6. Hull RD, Hirsh J, Carter CJ, Jay RM, Dodd PE, Ockelford PA, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. Ann Intern Med. 1983;98(6):891-9.

7. Lensing AW, Prandoni P, Prins MH, Büller HR. Deep-vein thrombosis. Lancet. 1999;353(9151):479-85.

8. White RH, McGahan JP, Daschbach MM, Hartling RP. Diagnosis of deep-vein thrombosis using duplex ultrasound. Ann Intern Med. 1989;111(4):297-304.

9. Nchimi A, Ghaye B, Noukoua CT, Dondelinger RF. Incidence and distribution of lower extremity deep venous thrombosis at indirect computed tomography venography in patients suspected of pulmonary embolism. Thromb Haemost. 2007;97(4):566-72.

10. Kelly J, Hunt BJ, Moody A. Magnetic resonance direct thrombus imaging: a novel technique for imaging venous thromboemboli. Thromb Haemost. 2003;89(5):773-82.

11. Westerbeek RE, van Rooden CJ, Tan M, van Gils AP, Kok S, de Bats MJ, et al. Magnetic resonance direct thrombus imaging of the evolution of acute deep vein thrombosis of the leg. J Thromb Haemost. 2008;6(7):1087-92.

12. de Moerloose P, Reber G, Perrier A, Perneger T, Bounameaux H. Prevalence of factor V Leiden and prothrombin G20210A mutations in unselected patients with venous thromboembolism. Br J Haematol. 2000;110(1):125-9.

13. van Stralen KJ, Doggen CJM, Bezemer ID, Pomp ER, Lisman T, Rosendaal FR. Mechanisms of the factor V Leiden paradox. Arterioscler Thromb Vasc Biol. 2008;28(10):1872-7.

14. Manten B, Westendorp RG, Koster T, Reitsma PH, Rosendaal FR. Risk factor profiles in patients with different clinical manifestations of venous thromboembolism: a focus on the factor V Leiden mutation. Thromb Haemost. 1996;76(4):510-3.

15. Bounameaux H. Factor V Leiden paradox: risk of deep-vein thrombosis but not of pulmonary embolism. Lancet. 2000;356(9225):182-3.

16. Ordonez AJ, Carreira JM, Alvarez CR, Rodriguez JM, Alvarez MV, Coto E. Comparison of the risk of pulmonary embolism and deep vein thrombosis in the presence of factor V Leiden or prothrombin G20210A. Thromb Haemost. 2000;83(2):352-4.

17. Baglin TP, Brown K, Williamson D, Baker P, Luddington R. Relative risk of pulmonary embolism and deep vein thrombosis in association with the factor V Leiden mutation in a United Kingdom population. Thromb Haemost. 1997;77(6):1219.

18. Desmarais S, de Moerloose P, Reber G, Minazio P, Perrier A, Bounameaux H. Resistance to activated protein C in an unselected population of patients with pulmonary embolism. Lancet. 1996;347(9012):1374-5.

19. van Langevelde K, Flinterman LE, van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Broadening the factor V Leiden paradox: pulmonary embolism and deep-vein thrombosis as two sides of the spectrum. Blood. 2012

20. Makelburg AB, Veeger NJ, Middeldorp S, Hamulyak K, Prins MH, Büller HR, et al. Different risk of deep vein thrombosis and pulmonary embolism in carriers with factor V Leiden compared with non-carriers, but not in other thrombophilic defects. Results from a large retrospective family cohort study. Haematologica. 2010;95(6):1030-3.

21. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ. 2009;339b2921.

22. Schneider C, Bothner U, Jick SS, Meier CR. Chronic obstructive pulmonary disease and the risk of cardiovascular diseases. Eur J Epidemiol. 2010;25(4):253-60.

23. Ribeiro DD, Lijfering WM, van Hylckama Vlieg, Rosendaal FR, Cannegieter SC. Pneumonia and risk of venous thrombosis: results from the MEGA study. J Thromb Haemost. 2012

24. de Boer JD, Majoor CJ, van 't Veer C, Bel EH, van der Poll T. Asthma and coagulation. Blood. 2012

25. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293(6):715-22.

26. Moody AR. Magnetic resonance direct thrombus imaging. J Thromb Haemost. 2003;1(7):1403-9.

27. van Langevelde K, Tan M, Sramek A, Huisman MV, de Roos A. Magnetic resonance imaging and computed tomography developments in imaging of venous thromboembolism. J Magn Reson Imaging. 2010;32(6):1302-12.

28. Fraser DG, Moody AR, Morgan PS, Martel AL, Davidson I. Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. Ann Intern Med. 2002;136(2):89-98.

29. Coon WW, Coller FA. Clinicopathologic correlation in thromboembolism. Surg Gynecol Obstet. 1959;109:259-69.

30. Lindblad B, Sternby NH, Bergqvist D. Incidence of venous thromboembolism verified by necropsy over 30 years. BMJ. 1991;302(6778):709-11.

31. Velmahos GC, Spaniolas K, Tabbara M, Abujudeh HH, de Moya M, Gervasini A, et al. Pulmonary embolism and deep venous thrombosis in trauma: are they related? Arch Surg. 2009;144(10):928-32.

32. Cairoli E, Codina C, Cura L, Pino A, Alonso J. Atrial thrombus entrapped in a patent foramen oval. Report of one case. Rev Med Chil. 2008;136(6):753-6.

33. Myers PO, Fassa AA, Panos A, Licker M, Bounameaux H, Zender HO, et al. Life-threatening pulmonary embolism associated with a thrombus straddling a patent foramen ovale: report of a case. J Card Surg. 2008;23(4):376-8.

34. Sorensen HT, Horvath-Puho E, Lash TL, Christiansen CF, Pesavento R, Pedersen L, et al. Heart disease may be a risk factor for pulmonary embolism without peripheral deep venous thrombosis. Circulation. 2011;124(13):1435-41.

35. Pesavento R, Piovella C, Prandoni P. Heart disease in patients with pulmonary embolism. Curr Opin Pulm Med. 2010;16(5):415-8.

36. Prandoni P, Pesavento R, Sorensen HT, Gennaro N, Dalla VF, Minotto I, et al. Prevalence of heart diseases in patients with pulmonary embolism with and without peripheral venous thrombosis: findings from a cross-sectional survey. Eur J Intern Med. 2009;20(5):470-3.

37. Knudson MM, Gomez D, Haas B, Cohen MJ, Nathens AB. Three thousand seven hundred thirty-eight posttraumatic pulmonary emboli: a new look at an old disease. Ann Surg. 2011;254(4):625-32.

38. Yun AJ, Lee PY, Bazar KA. Can thromboembolism be the result, rather than the inciting cause, of acute vascular events such as stroke, pulmonary embolism, mesenteric ischemia, and venous thrombosis?: a maladaptation of the prehistoric trauma response. Med Hypotheses. 2005;64(4):706-16.

39. van der Poll T, Boer JD, Levi M. The effect of inflammation on coagulation and vice versa. Curr Opin Infect Dis. 2011;24(3):273-8.

40. Baglin T, Douketis J, Tosetto A, Marcucci M, Cushman M, Kyrle P, et al. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. J Thromb Haemost. 2010;8(11):2436-42.

41. Kovacs MJ, Kahn SR, Wells PS, Anderson DA, Chagnon I, le Gal G, et al. Patients with a first symptomatic unprovoked DVT are at higher risk of recurrent VTE than patients with a first unprovoked PE. J Thromb Haemost. 2010

42. Browse NL, Thomas ML. Source of non-lethal pulmonary emboli. Lancet. 1974;1(7851):258-9.

43. Gibbs NM. Venous thrombosis of the lower limbs with particular reference to bed-rest. Br J Surg. 1957;45(191):209-36.

44. Corrigan TP, Fossard DP, Spindler J, Armstrong P, Strachan CJ, Johnston KW, et al. Phlebography in the management of pulmonary embolism. Br J Surg. 1974;61(6):484-8.

45. Moser KM, LeMoine JR. Is embolic risk conditioned by location of deep venous thrombosis? Ann Intern Med. 1981;94(4 pt 1):439-44.

46. Monreal M, Ruiz J, Olazabal A, Arias A, Roca J. Deep venous thrombosis and the risk of pulmonary embolism. A systematic study. Chest. 1992;102(3):677-81.

47. Stern JB, Abehsera M, Grenet D, Friard S, Couderc LJ, Scherrer A, et al. Detection of pelvic vein thrombosis by magnetic resonance angiography in patients with acute pulmonary embolism and normal lower limb compression ultrasonography. Chest. 2002;122(1):115-21.

DOI: 10.3324/haematol.2012.069195

Table 1. Baseline characteristics of all PE patients.

PE patients	**N= 99**
Age (median, range in years)	54 (18-84)
Sex	
male	60 (61%)
female	39 (39%)
Body Mass Index (median, range in kg/m^2)	26 (16-39)
Hospital of origin	
Rijnland hospital	22 (22%)
LUMC	77 (78%)
In-hospital patients at time of diagnosis	20 (20%)
Duration of complaints (median, range in days)	2 (0-105)
Clinical ultrasound performed	13 (13%)
DVT on ultrasound	10 (77%)
No DVT on ultrasound	3 (23%)

DOI: 10.3324/haematol.2012.069195

Table 2. Localization of thrombi in PE patients with a DVT on MRI.

PE patients	**N= 99**
No thrombus on MRI	55 (56%)
Thrombus present on MRI	44 (44%)
Right leg DVT	13 (30%)
Left leg DVT	27 (61%)
Bilateral DVT	4 (9%)
1 vein	19 (43%)
2 veins	12 (27%)
3 veins	3 (7%)
4 veins	4 (9%)
5 veins	4 (9%)
6 or more veins	2 (5%)

DOI: 10.3324/haematol.2012.069195

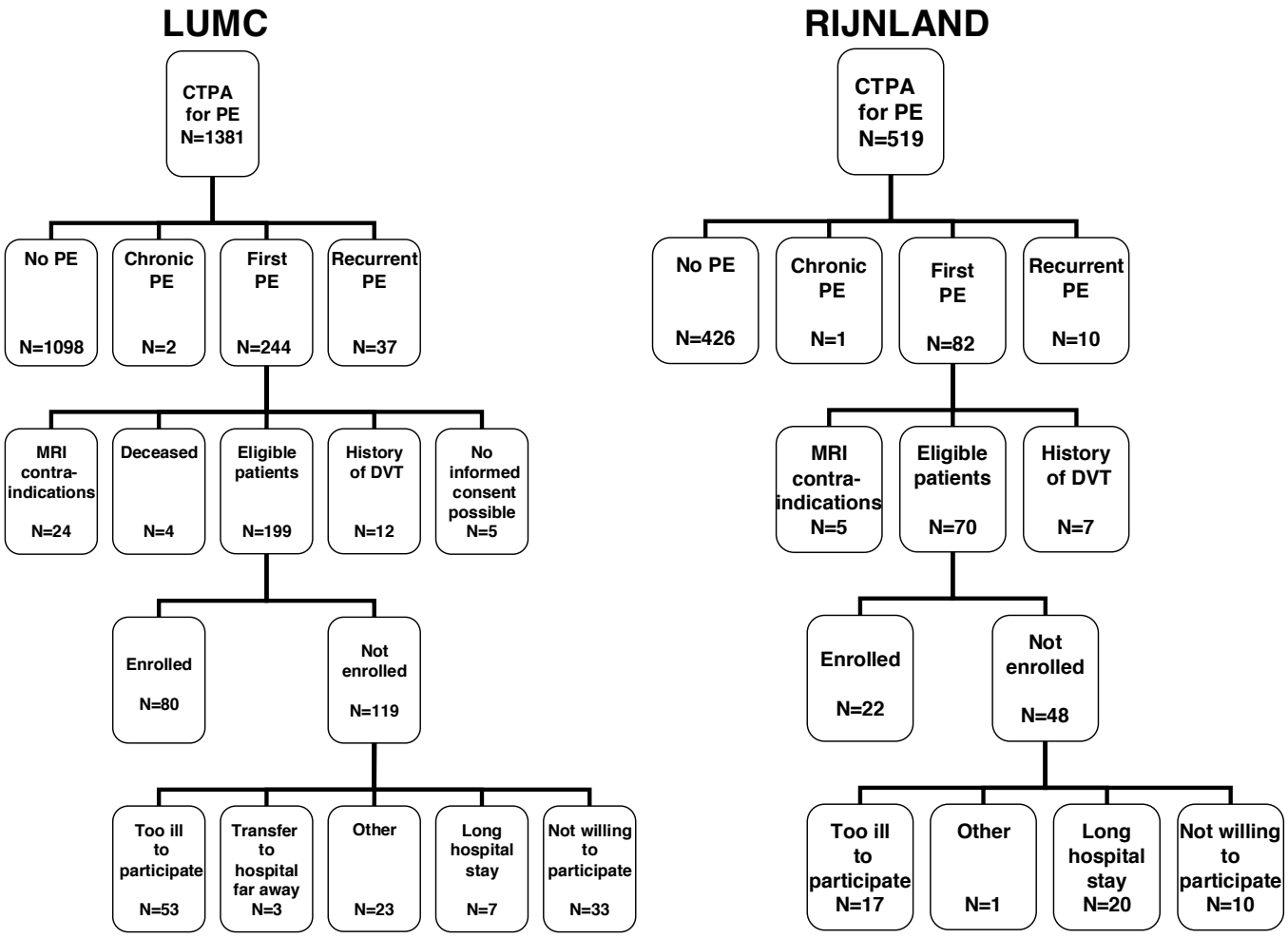
Table 3. Acquired and genetic risk factors for PE patients presenting with a thrombus on MRI and without a thrombus on MRI.

Risk factors	**Thrombus present on MRI** **N= 44** **n (%; 95% CI)**	**No thrombus on MRI** **N= 55** **n (%; 95% CI)**
Age >65 years	9 (20; 11-35%)	12 (22; 13-34%)
Malignancy		
history	4 (9; 4-21%)	6 (11; 5-22%)
active	10 (23; 13-37%)	13 (24; 14-36%)
Surgery in past 8 wks	9 (20; 11-35%)	13 (24; 14-36%)
Minor leg injuries in past 4 wks	5 (11; 5-24%)	3 (5; 2-15%)
Positive family history of VTE	11 (25; 15-39%)	10 (18; 10-30%)
Bedrest of >4 days in past 8 wks	7 (16; 8-29%)	15 (27; 17-40%)
Air travel of >8 hrs in past 8 wks	3 (7; 2-18%)	3 (5; 2-15%)
Travel of >4 hrs by car/train in the past 8 wks	4 (9; 4-21%)	9 (16; 9-28%)
Any immobilization factor	12 (27; 16-42%)	22 (40; 28-53%)
Women using contraceptive pill	4/17 (24; 10-47%)	7/22 (32; 16-53%)
Genetic risk factors	**N= 44**	**N= 54**
Factor V Leiden mutation		
heterozygous	6 (14; 6-27%)	3 (6; 2-15%)
homozygous	-	1 (2; 0-10%)
Prothrombin mutation		
heterozygous	1 (2; 0-12%)	2 (4; 1-13%)
homozygous	-	-

DOI: 10.3324/haematol.2012.069195

Figure 1. Study patients

Flowchart of patients with pulmonary embolism from the Rijnland Hospital and Leiden University Medical Center.



DOI: 10.3324/haematol.2012.069195

Figure 2. Anatomical distribution of thrombi on MRI

Division into seven venous segments with thrombosis in all patients with pulmonary embolism, with a deep-vein thrombosis on MR images (N=44).