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Thrombosis - Section 3

Controversies in treating small clots in the leg and in the lung

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Take-home messages

- Isolated distal DVT, and possibly subsegmental PE, are conditions that differ with regard to recurrence rate, mortality, and chronic sequelae from more extensive disease. A considerable proportion of both diagnoses is likely to represent false positive imaging results.
- Uniform anticoagulation for all patients has a substantial risk for an unfavorable harm-benefit-ratio.
- Risk profiling as basis for well-balanced treatment decisions is warranted but lacks firm data to be based on. All experts accept active cancer as high-risk condition necessitating anticoagulation. Others will have to be defined by future studies.

Introduction

'Small clots in the legs and in the lung' can be translated into two distinct disease entities, i.e. isolated distal calf vein thrombosis (ICVT) and subsegmental pulmonary embolism (SSPE). ICVT is being diagnosed mostly in symptomatic patients with suspected DVT. Thrombosis is confined to the calf muscle veins and/or the paired deep calf veins without involving the popliteal vein.

SSPE is being diagnosed in two different patient populations: first, in symptomatic patients, with the thrombembolus only in one or a few minor branch(es) of the pulmonary artery tree, supplying less than one segment; and second, in asymptomatic patients undergoing CT scans for follow up examinations in currently or previously treated cancer.

The clinical impact of small clots has been questioned in both cases, and thus, the need for anticoagulation is under debate.

Current state of the art

ICVT

Known from pathophysiology, most episodes of symptomatic deep vein thrombosis (DVT) start in the calf and propagate to the thigh veins.[1] Once having reached the proximal veins DVT has a considerable risk for pulmonary embolism. Conversely, as long as ICVT does not propagate the risk of pulmonary embolism (PE) is negligible.[2] Apart from propagation to proximal, ICVT is a relatively benign disease: recurrence rates are reportedly lower in ICVT than in proximal DVT or PE, except if associated with malignancy.[3] In addition, the frequency and severity of the post thrombotic syndrome (PTS) as a late sequela is less than half as compared with proximal DVT.[1]

The key question, therefore, is the estimated risk of propagation from distal to proximal. Different rates of extension of symptomatic ICVT to the proximal veins have been reported. A recent meta-analysis resulted in an estimate of around 9%.[4] This means that around 90% of all cases would not need anticoagulation because of a self-limiting natural course.[5]

Two different attitudes towards the diagnosis of DVT - and thereby ICVT - have emerged: serial imaging of the proximal leg veins with anticoagulation only in case of proximal DVT[6] *versus* complete compression ultrasound of the leg (CCUS) as a single examination,[7] followed by anticoagulation of proven ICVT in most cases. Neither the first nor the second strategy has proven superiority over each other regarding safety or efficacy.[8,9] However, serial testing of proximal veins is not resource saving, whereas routine examination of distal veins carries a substantial risk of overtreatment due to both false positive ultrasound results and anticoagulation of a self-limiting condition.

Up to now, randomized trials on treatment of ICVT failed to demonstrate any benefit of anticoagulation[10] (Table 1). The most recent example of such a RCT was the CACTUS trial that showed no difference in efficacy but significantly more

bleeding in patients with anticoagulation.[11] Like others, it suffered from the fact that only patients with an obviously low risk of propagation had been included. Consequently, international guidelines give only low-grade recommendations for a highly individualized treatment algorithm based on supposed risk factors for propagation.[12]

SSPE

With the event of multiple detector computed tomographic pulmonary angiography (CTPA) the rate of detection of subsegmental pulmonary embolism, due to higher resolution, has increased. In parallel, doubts have arisen as to whether these SSPEs deserve the same treatment as segmental or even more proximal PEs.[13] The source of uncertainty is threefold. First, false positive SSPE detection in CTPA remains a matter of concern.[14] Second, the safety of single detector vs multiple detector CTPA for the exclusion of PE seemed to be equal despite a rate of SSPE double as high in the latter, thereby providing indirect evidence that the 'missed' SSPEs in single detector CTPA had no prognostic relevance in the following three months.[15] Third, epidemiologic studies demonstrated an increasing rate of incident PEs over the years without an increase in mortality due to PE. This provides indirect evidence that the case fatality of PE dropped down, indicating that the surplus of PEs can attributed to benign and clinically less relevant cases.[16] In consequence, therapeutic anticoagulation for all patients with a SSPE diagnosis might have a significant potential for harm.

There are no randomized controlled trials addressing the issue. In 2012, a systematic review identified 60 patients with SSPE in whom anticoagulation was withheld. None of these patients suffered recurrent symptomatic VTE (PE or DVT) during a 3-month follow-up.[17] By contrast, indirect evidence for a greater clinical relevance of SSPE was provided by the finding that, in a large cohort of patients with suspected PE, the prevalence of risk factors, the 3 months' recurrence risk and mortality of 116 SSPE patients was similar to 632 with more proximal PE but dissimilar to 2980 patients in whom PE had been excluded.[18] All patients with SSPE in this series had received anticoagulation. This is in concordance with the result of a survey in which most experts were in favor of prescribing anticoagulants to patients with SSPE.[19] Finally, in a pooled cohort of 926 cancer patients with incidental PE from 11 different studies, 197 had had SSPE. Again, the 6 months' recurrence rate was similar to patients with incidental, more proximally located PE. In the subgroup of 42 patients left untreated, the recurrence rate of SSPE was numerically comparable between SSPE and other localisations.[20]

Like for ICVT, international guidelines support a management algorithm that takes risk factors for propagating or relapsing VTE into account when assessing the need for anticoagulation. Unequivocally, patients with active cancer are considered to be at high risk.

Future perspectives

Despite the lack of direct evidence, the expert view is consolidating that for both entities, ICVT as well as SSPE, anticoagulation is indicated in patients with active cancer. A potential for withholding anticoagulation, however, does exist for non-cancer patients without other high-risk constellations for VTE propagation or recurrence. However, the definition of 'high risk' is far from being established and is likely to be different in ICVT and SSPE. Since any RCT will require firm exclusion criteria a priori, no additional insights about 'high risk' can be gained from such type of future study. Instead, better knowledge may be derived from well-characterized cohorts of patients with either ICVT or SSPE who are left untreated but receive close surveillance in order to attribute adverse outcomes to given risk factor profiles.

References

1. Kearon C. Natural history of venous thromboembolism. Circulation 2003;107(23 Suppl 1):I22-30.
*2. Palareti G, Cosmi B, Lessiani G, et al. Evolution of untreated calf deep-vein thrombosis in high risk symptomatic outpatients: the blind, prospective CALTHRO study. Thromb Haemost 2010;104:1063-1070.
The design of this particular cohort study is unique and provides the up to now most close look on the natural history of ICVT.
3. Galanaud JP, Quenet S, Rivron-Guillot K, et al. Comparison of the clinical history of symptomatic isolated distal deep-vein thrombosis vs. proximal deep vein thrombosis in 11 086 patients. J Thromb Haemost 2009;7:2028-34.
4. Garry J, Duke A, Labropoulos N. Systematic review of the complications following isolated calf deep vein thrombosis. Br J Surg 2016;103:789-96.
5. Palareti G, Schellong S. Isolated distal deep vein thrombosis: What we know and what we are doing. J Thromb Haemost 2012;10:11-19.
6. Cogo A, Lensing AW, Koopman MM, et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. BMJ 1998;316:17-20.
7. Johnson SA, Stevens SM, Woller SC, et al. Risk of deep vein thrombosis following a single negative whole-leg compression ultrasound: a systematic review and meta-analysis. JAMA 2010;303:438-45.
8. Bernardi E, Camporese G, Buller HR, et al. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. JAMA 2008;300:1653-59.
9. Gibson NS, Schellong SM, Kheir DY, et al. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous

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thrombosis: a prospective management study. J Thromb Haemost 2009;7:2035-41.

10. Masuda EM, Kistner RL, Musikasinthorn C, et al. The controversy of managing calf vein thrombosis. J Vasc Surg 2012;55:550-61.

*11. Righini M, Galanaud JP, Guenneguez H et al. Anticoagulant therapy for symptomatic calf deep vein thrombosis: the CACTUS randomised placebo-controlled trial. Lancet Haematol 12; 2016:e556-e562.

This is the largest and methodologically most profound RCT for ICVT – not yet included in the ACCP 2016 document (ref 12), illustrating the inclusion bias towards low risk ICVT patients.

*12. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. Chest 2016; 149:315-52.

This document gives the most widely accepted view on the treatment of ICVT as well as of SSPE, based only on high quality data.

13. Le Gal G, Righini M, Parent F, et al. Diagnosis and management of subsegmental pulmonary embolism. J Thromb Haemost 2006; 4:724-31.

14. Pena E, Kimpton M, Dennie C, et al. Difference in interpretation of computed tomography pulmonry angiogaphy diagnosis of subsegmental thrombosis in patients with suspected pulmonary embolism. J Thromb Haemost 2012;10:496-8.

15. Carrier M, Righini M, Wells PS, et al. Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. J Thromb Haemost. 2010; 8:1716-22.

*16. Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. BMJ. 2013; 347:f3368.

This is a landmark article, summarizing the dilemma of detecting by a very high sensitive test a disease which may not be worthwhile treating.

17. Carrier M1, Righini M, Le Gal G. Symptomatic subsegmental pulmonary embolism: what is the next step? J Thromb Haemost 2012;10:1486-90.

18. den Exter PL, van Es J, Klok FA, et al. Risk profile and clinical outcome of symptomatic subsegmental acute pulmonary embolism. Blood 2013;122:1144-9.

19. den Exter PL, van Roosmalen MJ, van den Hoven P, et al. Physicians' management approach to an incidental pulmonary embolism: an international survey. J Thromb Haemost 2013;11:208-13.

*20. van der Hulle T, den Exter PL, Planquette B, et al. Risk of recurrent venous thromboembolism and major hemorrhage in cancer-associated incidental pulmonary embolism among treated and untreated patients: a pooled analysis of 926 patients. J Thromb Haemost 2016;14:105-13.

This very large pooled patient series strongly supports the view that at least in cancer patients SSPE does require treatment comparable to symptomatic more proximal PE.