Imaging techniques for ageing deep vein thrombosis: a systematic review

Poster No.: C-1434
Congress: ECR 2015
Type: Scientific Exhibit
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Keywords: Vascular, Veins / Vena cava, Ultrasound, MR, Experimental investigations, Haematologic diseases
DOI: 10.1594/ecr2015/C-1434

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Aims and objectives

Deep vein thrombosis (DVT) is common with an incidence of 1 in 1,000 person-years (1,2). It is characterised by symptoms of limb swelling, pain, erythema and warmth. In the United Kingdom it is responsible for 25,000 deaths per year usually as a result of pulmonary embolism (PE) (3). Those that survive life threatening episodes commonly require lifelong anticoagulation and up to 50% develop post thrombotic syndrome (PTS). PTS can lead to significant morbidity from reduced quality of life with ulceration observed in up to 10% of cases.

Clinical assessment of DVT is proven to be unreliable (4). Risk stratification assessment tools such as the Wells score provide guidance for further investigation for diagnosis of DVT, however, do not take into account the age of the thrombus (5,6) Similarly, venous Duplex ultrasonography, which is the current gold standard first line investigation for imaging DVT, is unable to differentiate between acute and chronic thrombi.

The need for accurate ageing of DVT has been highlighted recently by the introduction of endovascular techniques of acute thrombus removal for extensive proximal DVT in order to reduce the burden of PTS. Catheter directed thrombolysis (CDT) and pharmacomechanical thrombolysis enable rapid, local lysis of thrombus, preserving the vessel lumen and valvular function which is not achieved by conventional anticoagulation therapy. However, current guidance in the USA and UK only recommends thrombus removal within the first 14 days (7,8)

Several promising imaging techniques have emerged in an attempt to estimate thrombus age in an objective, accurate and cost effective manner that may be employed in a clinical setting. The aim of this systematic review is to collate and evaluate experimental and clinical evidence regarding these modalities.
Methods and materials

Systematic review following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines was performed (9). PubMed and EMBASE databases were searched from 1948 up until September 2013 by two reviewers independently. The following, agreed search terms were employed: 'deep vein thrombosis ageing', 'deep vein thrombosis age', 'deep vein thrombosis stage', 'deep vein thrombosis staging', 'deep vein thrombosis imaging', 'deep vein thrombosis staging imaging', 'deep vein thrombosis aging imaging'. Articles were eligible for inclusion if study endpoints included assessment of age of venous thrombi using imaging techniques. Review articles, case studies, editorials, letters, articles not in English and duplicates were all excluded. Manual searching of reference lists from publications included in the full-text stage of the review was also performed. Data was extracted under the following headings: thrombosis aging modality, experimental or clinical setting, study design, thrombus ages assessed and thrombus aging outcomes.
Results

Figure 1 represents the PRISMA diagram summarising search results of the systematic review. The search terms returned 13,374 articles. Following the complete screening process 15 studies were included for review.

Search results highlighted elastography and Magnetic Resonance Imaging (MRI) as the two most investigated imaging modalities for ageing DVT, with 8 and 3 studies being reviewed for each modality respectively. Articles assessing other modalities such as photoacoustic and nuclear imaging were also identified. Significant heterogeneity in study design across all articles did not allow quantitative data synthesis. Table 1 summarises the data and outcomes from ultrasound related studies, whilst Table 2 summarises the data and outcomes from all other imaging modalities that were reviewed in full.

Ultrasonography related techniques

Ultrasonography related techniques have been the most investigated for aging of venous thrombosis thus far. Elastography is a non-invasive technique that differentiates between tissues of different elasticity, based on an estimation of strain during tissue compression and expansion. Emelianov et al. surgically induced 17 clots in 15 rats after which they were split into 3 even groups; kept for 2 days, 6 days or 9 days before undergoing ultrasound elasticity imaging studies. It was demonstrated that older clots were consistently harder and more regular than younger ones, which is consistent with results from subsequent studies also assessing this method of push elastography (10,11).

Clinical studies using elastography and strain analysis have also shown promise. Rubin et al. performed a prospective human study of 54 patients; 26 with acute DVT (mean age 5.7 days) and 28 with chronic DVT (mean age > 8 months) (12). It was shown that the median normalised strain magnitude for acute cases was 2.78 (Interquartile Range (IQR): 2.4-3.71), compared to 0.94 (IQR: 0.48-1.36) in chronic cases with a median relative echogenicity of 1.4 (IQR: 1.17-1.54) for acute thrombi and 4.5 for chronic thrombi (IQR 2.5-7.5).

Novel dynamic methods that use standardised propagation of mechanical waves such as shear wave elastography may enable improved quantification and reproducibility (13-15).

Magnetic Resonance Imaging
Early studies to use MRI to age DVT included Froehlich et al. who used Gadolinium enhanced magnetic resonance venography (MRV) (16). The rim-centre ratio comparing the signal intensity at the rim of the vessel to that at the centre of the vessel, dropped significantly over time from a mean of 2.38 ± 0.17 over the first 14 days of the DVT to 1.29 ± 0.44 in images performed over next 14 days.

Westerbeek et al. assessed 43 consecutive patients with a first episode of acute DVT, in an attempt to determine MR signal change in the 6 months following presentation (17). Using Magnetic Resonance Direct Thrombus Imaging, normalisation of hyper-intensive T1 signal occurred in 90% of patients within 3 months and 100% of patients over a 6 month period.

Recently, Phinikaridou et al. compared in vivo MRI analysis with thrombus histology using a murine model of DVT (18). Magnetic transfer (MT) and diffusion weighted imaging (DWI) MRI were able to visualise and detect the thrombus protein composition, thereby allowing staging of the DVT. The MT rate correlated with histologically confirmed protein thrombus content and was significantly higher at days 14, 21 and 28. Combined analysis of both MT and DWI MRI imaging was able to demonstrate encouraging sensitivity and specificity for the identification of sub-acute aged thrombi in this model.

Other Imaging Modalities

Nuclear medicine techniques have also been explored. Bates et al. used radiolabelled glycoprotein IIb/IIIa expressed in activated platelets, which are particularly plentiful in acute DVT (19). It was determined that there was 92% sensitivity and 82-90% specificity between two expert readers in determining between acute and chronic thrombi. Brighton et al. confirmed that uptake of Technetium 99m labelled tissue plasminogen activator (rt-PA) into DVT was absent in patients on day 30 who had initially presented with an acute DVT in whom there was positive uptake on day 7 (20). This was attributed to fewer fibrin sites available for rt-PA binding as thrombi progress from acute to chronic state.

Photoacoustic imaging, a technique capable of non-invasive measurements of optical absorption in tissue, may be feasible to assess changes at a cellular and molecular level within a thrombus. Experimental studies suggest that the decrease in the fraction of blood cells in the clot over time may be exploited to clinical benefit with the magnitude of the photoacoustic signal being inversely proportional to the age of the clot (21,22).
Fig. 1: PRISMA Diagram

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<table>
<thead>
<tr>
<th>Study, year</th>
<th>Ultrasound technique</th>
<th>Study setting</th>
<th>Thrombus model</th>
<th>Thrombus ages</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parsons et al. 1993</td>
<td>Colour Doppler Ultrasound</td>
<td>In vivo</td>
<td>Forcine jugular vein</td>
<td>30 minutes, 1.7 &amp; 14 days</td>
<td>Differences in ultrasonic tissue characterisation of thrombi statistically significant for thrombi at day 7 and day 14, P&lt;0.01</td>
</tr>
<tr>
<td>Emelianov et al. 2002</td>
<td>Elastography</td>
<td>In vivo</td>
<td>Rat IVC</td>
<td>2.6 &amp; 9 days</td>
<td>Normalised strain measurements show increased clot Young's modulus demonstrated over days 2.6 &amp; 9 as it hardens, matures and organizes</td>
</tr>
<tr>
<td>Rubin et al. 2003</td>
<td>Elastography</td>
<td>Clinical</td>
<td>Lower limb DVT</td>
<td>25 days &amp; 3 years</td>
<td>Chronic clot homogeneous with strain 10 smaller than vessel wall. Subacute clot heterogeneous with strain x=4 greater than vessel wall (n=2)</td>
</tr>
<tr>
<td>Xie et al. 2004</td>
<td>Elastography</td>
<td>In-vivo</td>
<td>Rat IVC</td>
<td>3.4, 5.6, 7 &amp; 10 days</td>
<td>Strain magnitude progressively decreases as clot ages. Using normalisation from vessel wall, clot age could be estimated to within 0.8 days</td>
</tr>
<tr>
<td>Aglyamov et al. 2004</td>
<td>Elastography</td>
<td>In-vitro &amp; in vivo</td>
<td>Gelatin phantom &amp; rat IVC</td>
<td>2 &amp; 9 days</td>
<td>Circular simulation model developed for mechanical measurement in-vitro for improved elasticity reconstruction is feasible to provide accurate measurements of ageing for real world elliptical vessel and clot as found in-vivo and clinically</td>
</tr>
<tr>
<td>Xie et al. 2005</td>
<td>Elastography</td>
<td>In-vivo &amp; ex-vivo</td>
<td>Rat IVC</td>
<td>3.6, 10, 12 &amp; 14 days</td>
<td>Direct mechanical measurement of Young's modulus shows good temporal agreement up to 10 days in both ex-vivo and in vivo conditions</td>
</tr>
<tr>
<td>Giese et al. 2005</td>
<td>Elastography</td>
<td>Ex-vivo</td>
<td>Explanted porcine iliac vein</td>
<td>1.3, 6, 9, 12 &amp; 15 days</td>
<td>Significant decline in mean thrombus strain between days 6 &amp; 12, P&lt;0.01. Three-fold increase in hardness correlated to increase in fibroblast and collagen histologically</td>
</tr>
<tr>
<td>Karpiont et al. 2005</td>
<td>Photoacoustic</td>
<td>In-vitro</td>
<td>Phantom clot preparations (RBC, PVA &amp; Silica)</td>
<td>Acute &amp; Chronic</td>
<td>Strong photoacoustic signals obtained from acute clots due to increased RBC optical absorption compared to reduced magnitude of signal from fewer RBC in chronic clot</td>
</tr>
<tr>
<td>Rubin et al. 2006</td>
<td>Elastography</td>
<td>Clinical</td>
<td>Lower limb DVT</td>
<td>Acute (&lt;14 days) &amp; Chronic (&gt;18 months)</td>
<td>Median normalized strain value in acute group was 2.78 (n=26) and in the chronic group was 0.94 (n=28) which was highly significant, P&lt;0.01</td>
</tr>
<tr>
<td>Karpiont et al. 2008</td>
<td>Photoacoustic</td>
<td>In-vitro &amp; ex-vivo</td>
<td>Human venous blood &amp; explanted rat IVC</td>
<td>3 &amp; 9 days</td>
<td>Linear relationship between RBC clot concentration and magnitude of photoacoustic signal in-vitro. Photoacoustic magnitude profile considerably different between day 3 and day 9 clot</td>
</tr>
</tbody>
</table>

**Table 1:** Characteristics of included studies for DVT ageing using ultrasound related techniques

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Table 2: Characteristics of included studies for DVT ageing using MRI and nuclear imaging techniques

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Conclusion

This systematic review demonstrates the significant heterogeneity in data available for imaging techniques in the assessment of DVT ageing. Acute thrombus removal for extensive DVT highlights the importance of a reliable imaging tool for the staging of DVT to eliminate reliance upon a patient's history. Ultrasound elastography could be implemented as a simple and cheap adjunct to Duplex ultrasound to broadly distinguish between acute and chronic thrombi. Specific MRI sequences provide objective assessment of acute, sub-acute and chronic thrombi whilst providing complete assessment of the lower limb, pelvic and abdominal vessels, thus providing a comprehensive temporal and anatomical guide for acute interventions such as CDT. Both techniques warrant further validation of accuracy and reproducibility as they fall within current clinically utilised imaging modalities for vascular imaging.
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