Experimental venous thrombi: MRI characteristics with histopathological correlation

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Objectives: The purpose of this study was to evaluate the MRI characteristics of venous thrombus over set time thresholds with histopathological correlation in a porcine model.

Methods: Inferior vena cava thrombi were induced in 12 pigs. MRI was performed in three pigs 2 h, 1 day, 3 days and 2 weeks after thrombus induction.

Results: The MRI characteristics were analysed in correlation with histopathological findings. The thrombi after 2 hours, which consisted of red blood cells (RBCs), showed isointensity on T_1 weighted images (T_1 WIs) and hyperintensity on both T_2 weighted images (T_2 WIs) and diffusion-weighted images (DWIs). The mean apparent diffusion coefficient (ADC) value was $1.93 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. The thrombi after Day 1, which consisted of RBCs and migrating neutrophils at the periphery, showed isointensity on T_1 WIs, slight hyperintensity on T_2 WIs and hypointensity on DWIs. The mean ADC value was $1.62 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. The thrombi after Day 3, which consisted of RBCs and peripheral inflammatory cells including macrophages, showed isointensity with peripheral hyperintense regions on T_1 WIs and hypointensity on both T_2 WIs and DWIs. The mean ADC value was $1.67 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. After 2 weeks, the thrombi, which revealed RBC lysis surrounded by granulation tissues, showed isointensity on T_1 WIs and hyperintensity on T_2 WIs and DWIs. The mean ADC value was $2.48 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$.

Conclusion: The temporal MRI characteristics seemed to be related to chemical and physical changes in RBC and organisation of granulation tissues. Free radicals generated by macrophages might also be related to some extent.

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Deep vein thrombosis (DVT) is closely related to pulmonary thromboembolism (PTE), more than 90% of which probably originates from DVT of the lower extremities. Venous thromboembolism consists of PTE and DVT. Although PTE is a life-threatening disease, the survival rate can be improved with appropriate treatment [1–5]. For this reason, the precise diagnosis of DVT (the cause of PTE) is important for planning treatment.

There are various imaging techniques employed in the diagnosis of DVT, each of which has its own advantages and disadvantages, including sensitivity, specificity, invasiveness, radiation exposure, operator dependency and cost. Among them, MRI is a minimally invasive and reproducible modality, which has been applied using a variety of techniques. While most MRI techniques depict vessels as hyperintense structures and capture thrombi as signal voids [6–11], other techniques are aimed at directly visualising venous thrombi [12–14] and, in combination with each other, are expected to improve imaging characterisation.

Similarly to arterial thrombosis, the fundamental predisposing factors to venous thrombosis include the Virchow's triad, namely a hypercoagulable state, vascular intimal damage and stasis. Stasis seems to play the most important role in thrombus formation based on the physiological and anatomical venous character [15]. *In vivo* studies with animal models of venous thrombosis using MRI have already been reported [16–18]. In those studies, venous thrombi were induced by thrombin injection or by electric stimulation to the vessel. However, the thrombi seem to be histopathologically different from naturally formed thrombi and the studies failed to provide in-depth comparison of MRI and histopathological findings. In this study, we experimentally induced venous thrombi in pigs using balloon catheters to occlude the inferior vena cava (IVC) and evaluated signal intensities in T_1 weighted images (T_1 WIs), T_2 weighted images (T_2 WIs) and diffusion-weighted images (DWIs) in correlation with histopathological findings.

Methods and materials

All animals were used with the approval of the institutional animal care and use committee.

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Animals

12 female pigs (cross-bred hybrids of 3 swine strains) with a mean body weight of 20.2 kg (range, 17.0–24.8 kg) were used.

Methods

Inferior vena cava thrombi inductions with balloon catheters

The animals were given no food for 24 h prior to the procedure. Anaesthesia was induced with an intramuscular injection of midazolam ($40 \mu\text{g kg}^{-1}$), medetomidine hydrochloride ($50 \mu\text{g kg}^{-1}$) and ketamine hydrochloride ($10\text{--}20 \text{mg kg}^{-1}$) and maintained with a continuous infusion of pentobarbital sodium ($25 \text{mg kg}^{-1} \text{h}^{-1}$) into an ear vein as needed. With the use of anaesthesia and under sterile conditions, two 6-French balloon catheters with a maximum diameter of 20 mm (prototype; Clinical Supply, Gifu, Japan) were inserted, one into the right external jugular vein and the other into the right femoral vein, after access by means of surgical cut-downs. With fluoroscopic guidance, each catheter was advanced into the IVC and the right common iliac vein over a 0.035 inch J-shaped guidewire (Terumo, Tokyo, Japan). The IVC segment between the confluence of the common iliac veins and renal veins was visualised by a contrast medium injected into the right common iliac vein. The balloon of each catheter was inflated to form a 2 cm-long patent lumen in the IVC distal to the renal veins. After confirmation of the absence of branches by contrast venography, the IVC was occluded for 20 min. After deflation of the distal balloon, the thrombus induction was confirmed as a filling defect with accompanying collateral flow by manual venography (Figure 1). To maintain IVC occlusion, the distal balloon was inflated again and each catheter was kept in place. The skin incisions were closed with sutures.

MRI

MRI was performed 2 h, 1 day, 3 days and 2 weeks after thrombus induction in three pigs at each time interval under the above-mentioned general anaesthesia using a 1.5T instrument (Signa Advantage; GE Medical Systems, Milwaukee, WI) and a body coil. First, sagittal T_2 weighted localiser images were obtained to determine the position using the balloons as a guide and then axial spin-echo T_1 WIs [repetition time (TR), 500 ms; echo time (TE), 8.0 ms; field of view, 26×26 cm; matrix, 256×224 ; slice thickness, 4.0 mm; gap, 0.0 mm; number of excitation (NEX), 2], axial fast spin-echo T_2 WIs (TR, 4000 ms; TE, 98.0 ms; field of view, 26×26 cm; matrix, 256×224 ; echo train length, 8; bandwidth, $125.0 \text{ Hz pixel}^{-1}$; slice thickness, 4.0 mm; gap, 0.0 mm; NEX, 2) and axial single shot spin-echo echo-planar DWIs (TR, 5000 ms; TE, 98.7 ms; field of view, 26×26 cm; matrix, 128×128 ; slice thickness, 4.0 mm; gap, 0.0 mm; b value, 0, 400 s mm^{-2} ; NEX, 5) were obtained under free breathing. DWIs were acquired with diffusion sensitisation gradients applied in three orthogonal directions. An apparent diffusion coefficient (ADC) map was used for each ADC measurement. Circular regions of interest of 25 mm^2 were positioned

Figure 1. A postero-anterior venogram obtained immediately after inferior vena cava occlusion to form patent lumen for 20 min demonstrates a filling defect as thrombus induction (arrows), with accompanying collateral flow (arrowheads).

between the balloons corresponding to venous thrombi on the ADC map. ADC values were measured five times and the minimal value was selected. Fat suppression imaging, such as the chemical shift selective or the short tau inversion recovery techniques, was not used because misregistration and T_1 effects could interfere with reliable image interpretation.

Histopathological examinations

Immediately after MRI, the animals were euthanised by intravenous (iv) injection of pentobarbital sodium (100–150 mg). The abdominal wall was incised in mid-line to expose the IVC. The balloon occluded portion was resected together with balloons. The resected IVC was incised transversally to confirm the thrombus. After fixing the samples in formalin, transverse sections were made at 5 mm intervals. The samples were then embedded in paraffin and cut into sections of $4 \mu\text{m}$ thickness and stained with haematoxylin–eosin, elastica van Gieson and phosphotungstic acid haematoxylin.

Analysis

In each group, the signal intensities of the thrombus were compared with those of the muscle in the back on T_1 WIs, T_2 WIs and DWIs by two observers. Based on their consensus, MRI characteristics were analysed in correlation with histopathological findings.

Results

2 h after thrombus induction

The thrombi showed isointensity on T_1 WIs and hyperintensity on T_2 WIs. On DWIs (Figure 2) the thrombi showed hyperintensity in two pigs, but were not evaluated in one pig because of an artefact. The ADC values in these two pigs were $1.91 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ and $1.95 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. Macroscopically, the thrombi were dark red in colour, and microscopically they consisted of red blood cells (RBCs).

Day 1 after thrombus induction

The thrombi showed isointensity on T_1 WIs, slight hyperintensity on T_2 WIs and hypointensity on DWIs (Figure 3). ADC values were $1.37 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, $1.67 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ and $1.82 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. Macroscopically, the thrombi were dark red in colour, and microscopically they consisted of RBCs and neutrophils at the periphery.

Day 3 after thrombus induction

On T_1 WIs, most of the thrombi showed isointensity except at the periphery, where hyperintensity was seen (Figure 4). On both T_2 WI and DWI, they showed hypointensity. ADC values were $1.02 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, $2.13 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ and $1.87 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. Macroscopically, the thrombi were dark red in colour, and microscopically they consisted of RBCs and peripheral infiltration of fibroblasts in addition to inflammatory cells including macrophages.

2 weeks after thrombus induction

The thrombi showed isointensity on T_1 WIs and hyperintensity on T_2 WIs and DWIs (Figure 5). ADC values were $2.98 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, $2.25 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ and $2.21 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$. The thrombi were positioned at the central zone of the IVC macroscopically. Microscopic examinations revealed RBC lysis in the thrombi, which were surrounded by granulation tissues with collagen

Figure 2. MRI and histopathological examination 2 h after thrombus induction. The thrombus shows isointensity on (a) axial spin-echo T_1 weighted image [repetition time/echo time (TR/TE), 500/8.0] and hyperintensity on (b) axial fast spin-echo T_2 weighted image (TR/TE, 4000/98.0) and (c) axial single shot spin-echo echo-planar diffusion weighted image (TR/TE, 5000/98.7; b value, 400 s mm^{-2}) (arrows). (d) Photomicrograph shows red blood cell-based thrombus (haematoxylin-eosin stain; original magnification, $\times 40$). T, thrombus; V, vessel wall.

Figure 3. MRI and histopathological examination 1 day after thrombus induction. The thrombus shows isointensity on (a) axial spin-echo T_1 weighted image [repetition time/echo time (TR/TE), 500/8.0], slight hyperintensity on (b) axial fast spin-echo T_2 weighted image (TR/TE, 4000/98.0) and hypointensity on (c) axial single shot spin-echo echo-planar diffusion weighted image (TR/TE, 5000/98.7; b value, 400 s mm^{-2}) (arrows). (d) Photomicrograph shows neutrophils migrating into the peripheral portions of thrombus (arrows) (haematoxylin–eosin stain; original magnification, $\times 400$). T, thrombus; V, vessel wall.

fibres, elastic fibres and neovascular structures in addition to inflammatory cells. Haemosiderin-laden macrophages were also seen. The results are summarised in Table 1.

Discussion

Although various methods have been designed for venous thrombus induction based on the Virchow's triad [16–22], the majority of them produced thrombi by direct injection of coagulant factors or mechanical and/or chemical vessel wall damage. Stasis, however, is the most fundamental predisposing factor to venous thrombus formation. In the present study, we successfully induced venous thrombi in pigs with stasis by occluding the IVC with balloon catheters. 2 h of IVC occlusion induced RBC-based red thrombi, which were histopathologically similar to naturally formed fresh venous thrombi [23]. Our method is superior to other experimental methods because induced thrombi do not migrate, the cranial and caudal sides of the thrombi

were occluded with balloons and the vessel wall remains intact, which enables histopathological examination of natural thrombi.

After 2 h the thrombi showed hyperintensity on T_2 WIs and DWIs. Hyperintensity on DWIs was probably due to the influence of T_2 shine-through effects [24] rather than restricted water diffusion because of the high ADC values.

On T_2 WIs the thrombi showed slight hyperintensity after Day 1 and hypointensity after Day 3. These signal changes were probably caused by a decrease in free water protons as well as preferential T_2 proton relaxation enhancement due to high deoxyhaemoglobin concentrations. It was assumed, however, that the thrombi did not show hyperintensity on DWIs, probably owing to the T_2 blackout effect [25] and the lower b value used ($b=400 \text{ s mm}^{-2}$).

The peripheral portions of the thrombi after Day 3 showed a hyperintense rim on T_1 WIs. One of the most probable causes for this is methaemoglobin. Oxidation of deoxyhaemoglobin to methaemoglobin appears to be

Figure 4. MRI and histopathological examination from Day 3 after thrombus induction. Most of the thrombus shows isointensity, except for the peripheral portion which shows hyperintensity on (a) axial spin-echo T_1 weighted image [repetition time/echo time (TR/TE), 500/8.0] (arrow). The thrombus shows hypointensity on (b) axial fast spin-echo T_2 weighted image (TR/TE, 4000/98.0) and (c) axial single shot, spin-echo echo-planar diffusion-weighted image (TR/TE, 5000/98.7; b value, 400 s mm^{-2}) (arrows). (d) Photomicrograph shows the infiltration of fibroblasts in addition to inflammatory cells including the macrophages into peripheral portion of the thrombus (arrows) (haematoxylin-eosin stain; original magnification, $\times 400$). T, thrombus; V, vessel wall.

highly dependent on oxygen tension [26]. This process may have occurred at the peripheral portion of the thrombi in a pattern that reflected the oxygen diffusion gradient across the IVC wall, which receives its oxygen supply from the vasa vasorum [27]. Another possible cause is the generation of a large number of free radicals [28]. Histopathological examinations after Day 3 revealed fibroblasts in addition to a large number of inflammatory cells including macrophages in the peripheral portions of the thrombi. A large number of free radicals may have been generated by activated macrophages.

The thrombi after 2 weeks did not show hyperintensity on T_1 WIs, in contrast to our prediction based on previous studies [12, 13]. This is probably because of invasion of granulation tissues rather than oxidation of deoxyhaemoglobin to methaemoglobin, although macrophage activity waning is also a plausible explanation. Another cause may be that signals for methaemoglobin and free radicals were offset by collagen fibres, elastic fibres and haemosiderin, or

that deoxyhaemoglobin was insufficiently oxygenated to methaemoglobin because thrombi were not in contact with the blood flow. On DWIs, the thrombi after 2 weeks showed hyperintensity. The primary cause seemed to be the T_2 shine-through effects by RBC lysis due to the high ADC values. Although the observed granulation and neovascular tissues could also result in hypointensity on DWIs, these did not appear to be significant by histopathological observation.

To our knowledge, venous thrombus models in previous *in vivo* studies have been induced with thrombin injection or electric stimulation [16–18] and have shown signal patterns that are different from our study. It is possible that the thrombi observed in those studies have mainly consisted of platelets and fibrins [22]. In our study, porcine venous thrombi were red thrombi similar to the human venous thrombi [23] and the MRI characteristics were related to chemical and physical changes in RBCs and organisation of granulation tissues. Free radicals

Figure 5. MRI and histopathological examination 2 weeks after thrombus induction. The thrombus shows isointensity on (a) axial spin-echo T_1 weighted image [repetition time/echo time (TR/TE), 500/8.0], hyperintensity on (b) axial fast spin-echo T_2 weighted image (TR/TE, 4000/98.0) and (c) axial single shot, spin-echo echo-planar diffusion-weighted image (TR/TE, 5000/98.7; b value, 400 s mm^{-2}) (arrows). (d) Photomicrograph shows the thrombus that consists of red blood cell lysis surrounded by granulation tissue (haematoxylin–eosin stain; original magnification $\times 40$). T, thrombus; G, granulation tissue.

generated by macrophages may, to some extent, also be related. Although our induced thrombi were easily studied by MRI, because they were large in size and fixed

to the IVC, MR signal intensities may not be in accordance with those of clinically observed venous thrombi because in our technique thrombi were isolated from the blood

Table 1. Summary of the MRI and histopathological findings of the inferior vena cava thrombi

Group	T_1 WIs	T_2 WIs	DWIs	Mean ADC value ($\times 10^3 \text{ mm}^2 \text{ s}^{-1}$)	Histopathological findings
2 h	Isointensity	Hyperintensity	Hyperintensity ^a	1.93	Mainly red blood cells
Day 1	Isointensity	Slight hyperintensity	Hypointensity	1.62	Neutrophilic infiltration into the peripheral portions
Day 3	Most isointensity Peripheral hyperintensity	Hypointensity	Hypointensity	1.67	Fibroblastic and inflammatory infiltration into the peripheral portions
2 weeks	Isointensity	Hyperintensity	Hyperintensity	2.48	RBC lysis, granulation with inflammatory cells, fibres and neovascularities

ADC, apparent diffusion coefficient; DWIs, diffusion-weighted images; RBC, red blood cell; T_1 WIs, T_1 weighted images; T_2 WIs, T_2 weighted images.

^aThrombi after 2 h were not evaluated in one pig because of an artefact.

flow, whereas clinically observed thrombi were in contact with the blood flow; in other words, our thrombi would be in an environment of low oxygen tension. Our results, instead, may help to understand the temporal MR signal intensity changes of a venous thrombus in a large venous aneurysm, or a large haematoma in certain circumstances such as in an isolated space.

Among the studies focusing on DWI analysis of venous thrombosis, Favrole et al [29] reported the frequency of hyperintense thrombi on DWIs in a series of 28 patients with cerebral venous thrombosis (CVT). In their report, hyperintensity of venous thrombi was observed in 3 out of 14 cases within a few days of onset of thrombosis. Our thrombi, after days 1 and 3, however, were hypointense on DWI. This discrepancy could be explained by the fact that clinical manifestations of CVT are variable and do not coincide with radiological demonstration of venous thrombi [30].

Our experimental study had two important limitations. Firstly, the number of animals in each group was small. Future studies using a larger number of animals would be needed to confirm our findings. Secondly, DWI was performed with $b=400 \text{ s mm}^{-2}$ and was not performed with higher b values as in a previous investigation [31]. This was to preserve the signal-to-noise ratio owing to the large sized study materials; the MRI was performed under free breathing and the body coil was the best available. Signal intensities on DWIs at this $b=400 \text{ s mm}^{-2}$ may have been strongly influenced by the T_2 shine-through effect.

Conclusion

Experimental venous thrombi were formed by induced static blood flow in the IVC between two balloon catheters. Their temporal MRI characteristics were correlated with histopathological findings and seemed to be explained by chemical and physical changes in RBCs and organisation of granulation tissues. Free radicals generated by macrophages may, to some extent, also be related.

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