Detection of Intravascular Hematocrit in Equilibrium Phase Imaging Using a Blood Pool Agent

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Introduction: In a recent clinical study with the Vasovist™ (Epix Pharmaceuticals, Cambridge, MA; Schering AG, Berlin, Germany) blood pool agent, intravascular hematocrit (HCT) layering was detected on delayed imaging in patent calf veins. This phenomenon was more common in patients with known peripheral vascular occlusive disease (PVOD). Additional ex-vivo studies were performed using conventional and blood pool contrast agents to better understand and confirm the layering effect, as well as to study the effects of MR imaging parameters and intrinsic variables (T1, T2, and T2*) on HCT layering.

Methods: Six healthy volunteers and 5 patients with known PVOD received 0.03 mmol/kg of Vasovist in a phase II clinical study. Imaging was performed using a Philips NT 1.5T system with a 4 channel phased array coil. High resolution calf imaging was performed using a T1-FFE sequence approximately 30 minutes after contrast administration (TR/TE 15 ms/5 ms, flip 20°, matrix 432x712x80, FOV 440x308 mm^2, slice thickness 0.6 mm). Venous velocity was obtained using a 3D quantitative phase contrast (q-flow PC) sequence by cardiac-gating to acquire central k-space after peak systole (TR/TE 13 ms/5 ms, flip 20°, matrix 368x436x48, FOV 440x308 mm^2, slice thickness 1 mm, VENC 40 cm/s). Incidentally noted in multiple deep calf veins during the study was a mixing defect consisting of a layering between a more and less contrast-enhanced portions similar to filling defects that might be seen in DVT (Figs. 1-2). In one patient where this effect suggested focal DVT, a doppler ultrasound examination showed no thrombosis, and all study subjects were asymptomatic for DVT. It was hypothesized that the mixing defect was due to red blood cells (RBC) and plasma separating in slow flowing veins during the lengthy examination. To confirm this hypothesis, *ex-vivo* studies with blood pool (Vasovist) and conventional (Magnevist®, Berlex/Schering AG) contrast agents were conducted. Since velocity in veins demonstrating the HCT effect was slow (Table 1), static blood samples were imaged over the same time period as for the clinical study. Fresh blood from healthy volunteers was anti-coagulated and dispensed into syringes doped with Vasovist at 0.225, 0.45, and 0.75 mmol/L and Magnevist at 1.066, 2.13, and 3.55 mmol/L respectively. Vasovist concentrations were similar to those observed over the first hour following a 0.03 mmol/kg bolus used in the clinical study while Magnevist concentrations were chosen to approximate the same T1 relaxivity as Vasovist. Samples were imaged every 10 minutes for 60 minutes. Datasets were acquired using a 3D T1-FFE sequence at varying echo times (TR 18.5 ms, TE 1.8/5/10 ms) and a T2-weighted multiple spin-echo sequence (TR 4000 ms, TE 5/20/80/100 ms).

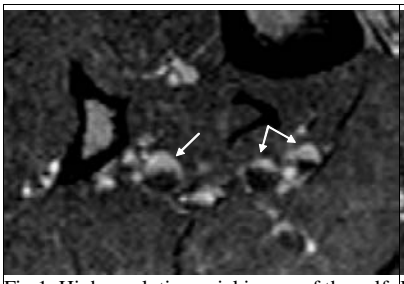

Fig 1. High resolution axial image of the calf showing HCT layering in multiple deep veins in a patient with PVOD given Vasovist.

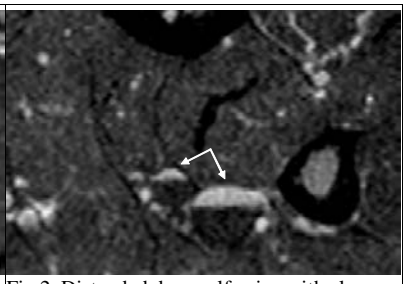

Fig 2. Distended deep calf veins with clear meniscus seen in HCT layering in a patient with PVOD.

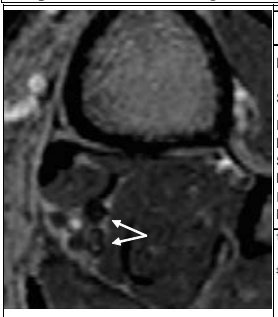

Fig 3. Complete non-enhancement in veins that lie inferior to HCT layering in a patient with PVOD.

Calf veins	No. of evaluated venous segments	Mean velocity (mm/s)	Variance	p-value†	
Normal deep veins	108	7.34	11.91		
Superficial veins	108	21.00	44.68	0.01	
Deep veins with layering	39	-0.56	3.26	0.001	
Superior enhanced layer in layering vein	39	1.10	2.58	0.001	0.1‡
Inferior less-enhanced layer in layering vein	39	-1.96	7.87	0.001	

† Velocities were compared with normal deep veins using a 2 sample t-test for independent samples and unequal variances, unless otherwise stated.
‡ P-value for paired t-test performed between the enhanced and less-enhanced layers of the vein.

Table 1. Velocity measurements in the lower extremity calf based on q-flow data.

Results: Intravascular HCT layering was seen in both the high resolution and q-flow PC images in 1 of 6 healthy subjects and all 5 patients. HCT layering only occurred in deep veins located in the middle to the posterior aspect of the calf and was more frequent in large veins. The higher signal layer was always in the non-dependent position of the vessel (Figs. 1-2), with plasma-to-RBC contrast ratios ranging from 1.3-4.7. Complete non-enhancement of some deep veins was detected (Fig. 3) caudal to veins showing HCT layering. Deep calf veins demonstrating the HCT effect had significantly slower flow than normal veins ($p = 0.001$), while the enhanced superior layer trended toward faster flow than the lesser-enhanced dependant layer (Table 1). In the *ex-vivo* study, initially homogeneous blood samples layered within 30 minutes. Both Vasovist and Magnevist showed similar enhancement patterns; the supernatant (plasma) layer of the contrast-doped samples was more enhanced than the dependent (RBC) layer (Fig 4). Contrast medium is more concentrated in plasma, shortening T1 to produce the layering effect observed in the clinical study. Iron present in hemoglobin shortens T2 and T2*, decreasing signal in the dependent layer, particularly as TE increases. At longer TE's, T2* shortening effects of the contrast become more influential in the higher concentration plasma layer, decreasing plasma-to-RBC signal ratio in the T1-FFE images (Fig 5).

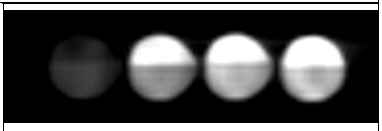

Fig 4. T1-FFE image with TE 1.8 ms showing HCT layering within an hour in blood samples doped with 0, 0.225, 0.45, and 0.75 mmol/L of Vasovist (left to right).

Discussion: Intravascular HCT layering effect has been observed once in the CT literature [1]. Using blood pool agents, intravascular HCT layering can clearly occur within a 30 to 60 minute imaging time frame. This type of layering occurs in larger, deeper veins with slower flow. As the effect was noted more in patients with PVOD, it is probable that poor circulation combined with venous enlargement contributes to this effect. Essentially identical enhancement patterns were observed using conventional contrast agents, as shown in the *ex-vivo* study. Plasma-to-RBC contrast was greater in the clinical study than the *ex-vivo* study, with ratios ranging 1.3 to 4.7 and 1 to 2.1 respectively. This may be due to more deoxyhemoglobin in the *in vivo* calf veins decreasing T2* and subsequently decreasing RBC layer signal. A second explanation is that separation of plasma and RBC may have already occurred pre-contrast administration, and because faster flow is seen in the superior plasma layer, more contrast is distributed to this region. Intravascular HCT layering is an under-recognized physiologic entity. It may be misinterpreted as DVT. This mistake need not be made as the enhanced layer is consistently located in the non-dependent part of the vein, and a clear meniscus is usually seen between the layers. When complete focal filling defects were seen, they a.) were caudal to regions of HCT layering, and b.) did not demonstrate wall enhancement, a hallmark of DVT, and hence should not be mistaken for DVT. Potential clinical applications may arise from the ability to detect diseased slow-flowing veins which may be associated with different vascular disease states. Additionally, HCT layering information may possibly be used as a perfusion metric or indicator of venous disease, since it appears to be associated with slow blood flow and poor venous return.

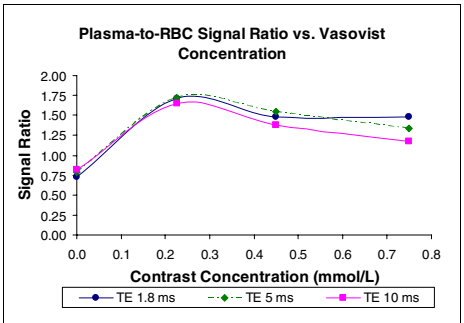

Fig 5. Plasma-to-RBC signal ratio in Vasovist in HCT at varying TEs. T2* effects are more pronounced at longer TEs.

References: 1. MC Lin *et al.*, J of Computer Assisted Tomography, 1991. **Acknowledgment:** This work was supported by Epix Pharmaceuticals Inc, Cambridge, MA.