"Bull's-eye" sign on gadolinium-enhanced magnetic resonance venography determines thrombus presence and age: A preliminary study

James B. Froehlich, MD, Martin R. Prince, MD, PhD, Lazar J. Greenfield, MD, L. Joseph Downing, MD, Nikhil L. Shah, BS, and Thomas W. Wakefield, MD, *Ann Arbor, Mich.*

Purpose: Venous thrombosis is associated with a significant inflammatory response, which can be visualized by gadolinium magnetic resonance venography (MRV). Gadolinium extravasates into tissue during inflammation, producing perithrombus enhancement on magnetic resonance scanning. This study determines (1) whether gadolinium enhancement occurs during deep venous thrombosis (DVT); and (2) whether this enhancement changes with time and can therefore establish the age of thrombus.

Methods: Patients with a diagnosis of iliofemoral DVT by duplex ultrasound who were referred for MRV to document central thrombus extent were studied. T1 weighted images were obtained before and after gadolinium injection (0.1 mmol/kg); repeat scans were obtained up to 3 months thereafter. At the level of maximum thrombus, measurements of signal intensity were made at the periphery (rim), and the center of the thrombosed vein, as well as the contralateral normal vein, on images after gadolinium enhancement. Rim-center vein signal intensity ratios were then calculated and followed.

Results: A total of 39 scans were obtained in 14 patients (eight men, six women). The thrombosed veins were enlarged, with a peripheral rim of enhancement ("bull's-eye" sign). The rim-center ratio for thrombosed veins (2.16 ± 0.18) was different from that of normal veins (0.66 ± 0.10; n = 39; $p < 0.001$). For all acute studies (≤14 days) the rim-center ratio was 2.38 ± 0.17 (n = 31), whereas for all chronic studies (>14 days) the rim-center ratio was 1.29 ± 0.44 (n = 8; $p = 0.001$). Among patients who underwent both early and late studies, the rim-center ratio dropped significantly, from 2.33 ± 0.20 acutely to 1.29 ± 0.44 in chronic studies (n = 8; $p = 0.03$). One patient with active malignancy had a paradoxic increase in rim-center ratio over time and a clinical recurrence of symptoms, suggesting active thrombosis.

Conclusions: We conclude that (1) a pattern of peripheral gadolinium enhancement (bull's-eye sign) is seen around acutely thrombosed veins on gadolinium-enhanced MRV, facilitating DVT diagnosis; and (2) the ratio of signal intensity at the rim versus the center of the thrombosed vein may be a good discriminator of acute compared with chronic DVT, which may help direct therapy. (J Vasc Surg 1997;26:809-16.)

From the Section of Vascular Medicine and Surgery, Department of Surgery; and the Division of Magnetic Resonance Imaging, Department of Radiology (Dr. Prince); University of Michigan Medical Center.

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Reprint requests: James B. Froehlich, MD, University of Michigan Medical Center, Section of Vascular Medicine, Division of Cardiology, Women's Hospital L3119, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0273.

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Venous thrombosis and resultant pulmonary embolism is the most common preventable cause of hospital death. It is estimated that as many as 150,000 to 200,000 people die each year of complications related to thromboembolism.[1] Because of this prevalence, much work has been focused on the diagnosis and treatment of deep venous thrombosis (DVT). Improved accuracy, as well as low risk and low cost, have made duplex ultrasound the standard test for the presence of venous thrombosis. It has an estimated sensitivity and specificity that exceed 95%.[1,2] Nonetheless, this method has limitations. Duplex ultrasound is not reliable in diagnosing iliac

Table I. Patient data

Patient	*Age (yr)*	*Sex*	*Symptoms*	*Diagnosis*	*Treatment*	*MRI day after diagnosis*							
						1	*3*	*5*	*7*	*14*	*21*	*30*	*90*
1	64	M	Rt. LE edema, 2-3 days	Trauma	Heparin and warfarin	X							
2	57	M	Rt. LE edema, 1 day	S/P femoropopliteal bypass grafting	Heparin and warfarin	X	X						
3	59	F	Not recorded	UC—S/P laparotomy	Not recorded	X			X		X		
4	54	M	Rt. LE edema <1 week	Pulmonary HTN/renal cell carcinoma	Heparin and warfarin	X		X		X			
5	89	M	Acute SOB, no edema	Prostate cancer	Heparin and warfarin	X							
6	57	M	Lt. LE edema, × 7 days	DVT	Heparin and warfarin	X							
7	72	F	Lt. LE edema, pain, acute SOB < 1 day	S/P PTA	Heparin and warfarin	X	X	X			X		
8	30	M	Lt. LE edema, × 2 days	Paraplegia	Heparin and warfarin	X		X		X			X
9	55	F	Rt. LE edema; tenderness, × 1 week	DM; norcardia; foot ulcers	Heparin and warfarin	X		X		X			
10	68	F	Rt. LE edema, × 3 days	AAA	Heparin and warfarin	X			X		X		X
11	66	F	Lt. LE pain, edema × 2 days	Ovarian cancer	Heparin and warfarin		X		X				X
12	60	F	Lt. LE edema, pain < 1 day	Raynaud's disease	Heparin and warfarin	X						X	
13	43	M	Lt. LE edema, < 1 week	CRF, DM	Heparin and warfarin	X	X		X	X			
14	67	M	Lt. LE edema, pain × 3 days	HTN, AF, S/P ureteroscopy	Heparin and warfarin	X		X	X				X

LE, Lower extremity; *SOB,* shortness of breath; *S/P,* status post; *UC,* ulcerative colitis; *HTN,* hypertension; *PTA,* percutaneous transluminal angioplasty; *DM,* diabetes mellitus; *AAA,* abdominal aortic aneurysm; *CRF,* chronic renal failure; *AF,* atrial fibrillation.

thrombosis because of difficulties in imaging above the inguinal ligament. Furthermore, criteria used for estimating the age of a venous thrombus by ultrasound are often not reliable. Therefore, identifying both the proximal extent and the age of some thrombi requires further testing. This is not an uncommon experience, as a history of previous DVT is among the most important risk factors for acute DVT.

Acute DVT elicits a strong inflammatory response in the vein wall and surrounding tissue at the site of the venous thrombus, characterized by an initial neutrophil infiltration followed by a monocyte macrophage extravasation into the vein wall.[3-6] Inflammation appears to be mediated by cytokines and adhesion molecules.[4] This inflammation may not only contribute to symptoms, but may also play a role in the pathogenesis of ongoing thrombosis. Magnetic resonance imaging (MRI) studies of experimentally induced thrombosis in animals suggest that the enhancement seen with gadolinium infusion corresponds to the areas of increased inflammation seen pathologically. Over time, the inflammation subsides. This suggests that the presence of vein wall and perivenous inflammation may discriminate acute from chronic DVT.

The purpose of this study was to identify how gadolinium-enhanced magnetic resonance venography (MRV) images change as acute DVT progresses to chronic DVT. It is our hypothesis that gadolinium enhancement may identify acutely thrombosed veins (with active inflammation) in clinical DVT and differentiate them from chronically thrombosed veins (without active inflammation). This may provide a mechanism for determination of thrombus age, a means for the diagnosis of acute DVT in the setting of a history of chronic venous thrombosis, and provide a method for evaluating the inflammatory response to venous thrombosis and interventions intended to modify this response.

MATERIALS AND METHODS

Patients greater than 18 years of age of either sex who were found on noninvasive testing in the Diagnostic Vascular Laboratory at the University of Michigan Medical Center to have significant iliofemoral vein thrombus were invited to participate in the study. Patients with iliac vein involvement were included selectively to focus on patients with thrombus in the same vein segment, and also because they had a clinical indication for the initial MRV study: to determine the central extent of thrombus. Only those patients in whom the proximal extent of thrombus could not be imaged with ultrasound were included. Subjects were excluded if they were unwilling or unable to undergo MRI scanning, (e.g.,

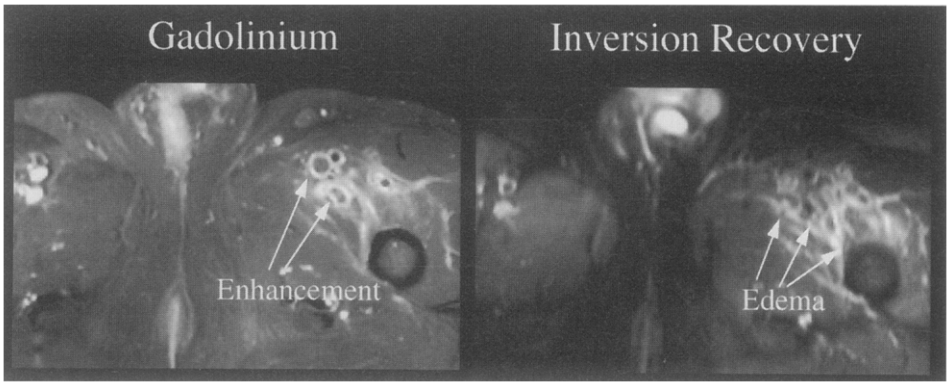

Fig. 1. Note enhancement on image after gadolinium injection *(left)* compared with inversion recovery image *(right)*. Enhancement with gadolinium was limited to vein wall, whereas edema *(bright signal on inversion recovery)* involved vein wall and perivenous tissue.

claustrophobia), if there was a contraindication to scanning (e.g., pacemaker), if they were immunosuppressed or immunocompromised for some reason, or if the thrombus was seen in its entirety and there was no question of central thrombus extent.

The study patients underwent an initial MRV study within 24 hours of diagnosis, followed by repeat scans on days 3, 5, 7, and 14 after diagnosis, as permitted by the patient's clinical status and care. Follow-up scans were obtained on an outpatient basis 3 months after diagnosis. Scans were performed with a 1.5 Tesla magnet (GE Medical Systems, Signa, Milwaukee). Time of flight, inversion recovery, T1, and T2 weighted images were obtained, as well as repeat T1 weighted images with fat saturation after intravenous infusion of gadopentetate dimeglumine (gadolinium) (0.1 mmol/kg, Berlex Laboratories, Wayne, N.J.). At the level of maximal clot involvement in the iliac vein, the diameters of the involved and contralateral uninvolved iliac veins were measured. The signal intensity was measured at the periphery (rim) and at the center of both the thrombosed and contralateral nonthrombosed veins, and a ratio of rim-to-center signal intensity was calculated for each of the vessels. These data were then plotted and analyzed over time both in aggregate and for individual subjects.

Statistical analysis was carried out using Mann-Whitney rank-sum, paired and nonpaired, nonparametric t tests for nonnormal distribution values, and paired and nonpaired Student's t test for the data that passed tests for normality. Values are indicated as mean ± the standard error of the mean. Tests used were two-tailed. A piecewise linear regression analysis was performed to determine whether there was a time-dependent breakpoint in the data. Informed consent was obtained from all of the study participants, and both the protocol and consent form were approved by the Institutional Review Board for Human Study of the University of Michigan Medical Center (protocol #IRB 94-544).

RESULTS

A total of 39 MRV scans were obtained in 14 patients, eight men and six women. This was less than the protocol called for, as a result of poor compliance, inability to successfully complete scans, and patient drop-out because of underlying medical problems. The patients' ages ranged from 30 to 89 years, with a mean of 60 years. Of the 14 patients, three had underlying malignancy, four had peripheral arterial occlusive disease, two had had traumatic injuries, and four had recently undergone surgery or invasive procedures (Table I). Only one patient had no identifiable underlying medical problem or risk factor for DVT.

On images obtained after gadolinium enhancement, all of the thrombosed veins were enlarged compared with the contralateral normal vein. The average diameter of the thrombosed veins was significantly greater than the nonthrombosed normal-side veins (16.3 ± 0.84 mm vs 13.5 ± 0.55 mm, respectively; $p = 0.01$). Images of thrombosed veins demonstrated bright signal on inversion recovery sequences, as well as enhancement of the thrombosed vein wall and perivenous tissue on images after gadolinium enhancement. The gadolinium enhancement was more intense in the vessel wall than the bright signal noted on inversion recovery images (Fig. 1). Gadolinium enhancement was greatest where thrombus was in contact with the vessel wall. In acutely thrombosed veins in which a flow channel

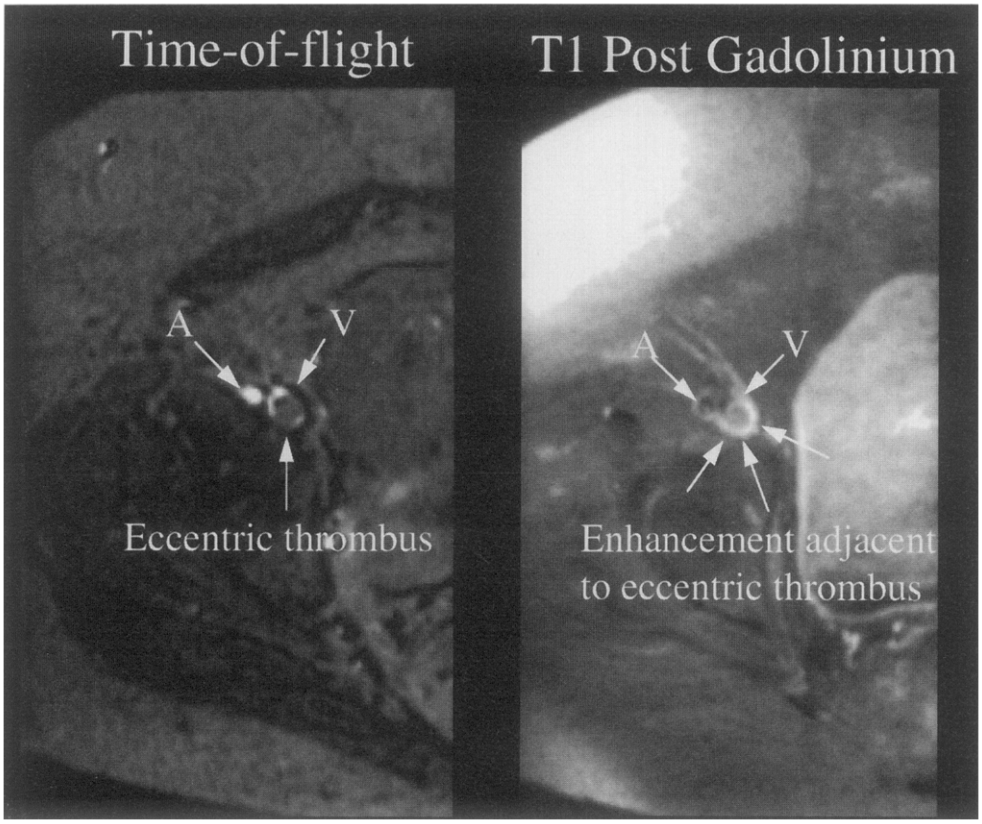

Fig. 2. Enhancement after gadolinium injection *(right)* occurred where thrombus was adherent to vein wall, whereas less enhancement was seen where flow channel was present on time-of-flight imaging *(left)*.

remained patent, enhancement was not noted in the area of the patent flow channel but only in the area of the adherent thrombus (Fig. 2).

Analysis of the imaged veins was made by calculating the ratio of the measured intensity at the rim of the vessel and dividing by the intensity at the center of the vessel on gadolinium-enhanced images. This rim-center ratio was then compared between the thrombosed and nonthrombosed vessels. This ratio was 2.16 ± 0.18 for all thrombosed veins and 0.66 ± 0.10 for contralateral normal veins ($n = 39$; $p < 0.001$).

Unlike the bright signal that is noted on inversion recovery imaging, the perivenous enhancement after gadolinium infusion decreased with time (Fig. 3). For studies performed within 14 days of diagnosis, the average rim-center ratio for the thrombosed vessel was 2.38 ± 0.17 ($n = 31$) compared with an average rim-center ratio of 1.29 ± 0.44 ($n = 8$) for studies performed greater than 14 days from the time of diagnosis ($p = 0.001$). This included one patient who had clinical evidence of recurrent thrombosis and an elevated rim-center ratio on a late study. Excluding this patient, the mean rim-center ratio for patients studied within 14 days of diagnosis was 2.34 ± 0.18 ($n = 29$), and for those studied greater than 14 days from the day of diagnosis 0.85 ± 0.11 ($n = 7$; $p < 0.001$). These data were then reanalyzed in a paired fashion, comparing studies performed within 14 days after diagnosis with only those studies performed in the same patients greater than 14 days after diagnosis. There were eight late (>14 days after diagnosis) scans performed in seven patients. These values were 2.33 ± 0.20 vs 1.29 ± 0.44 for early and late scans, respectively ($n = 8$; $p = 0.03$). Excluding the one patient with late clinical rethrombosis, these values are 2.25 ± 0.21 and 0.85 ± 0.11 ($n = 7$; $p < 0.001$; Table II).

A piecewise linear regression analysis of the rim-center intensity ratios for the thrombosed veins was then performed to determine whether there was a significant breakpoint in time after which the ratios became distinctly different. We first used this model to determine linearity of the rim-center data over

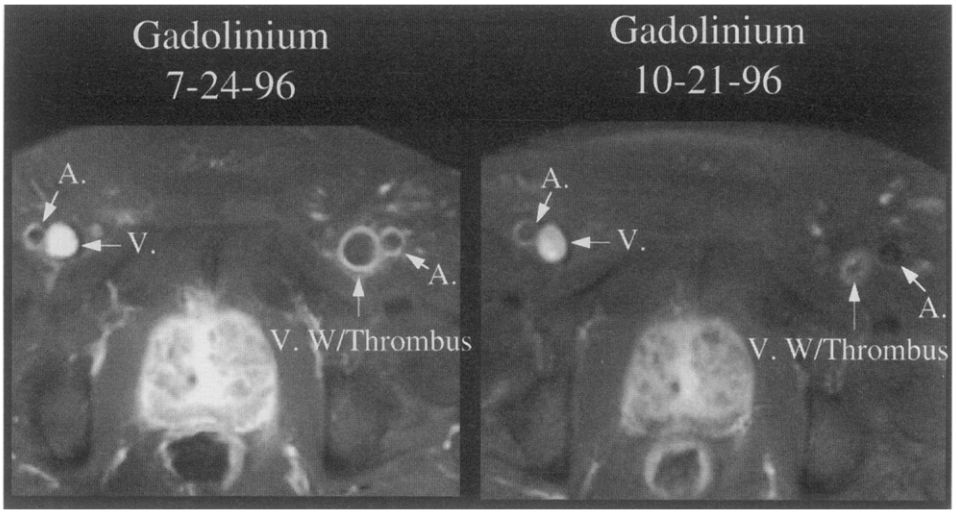

Fig. 3. Note that gadolinium enhancement that acutely *(left)* produced characteristic "bull's-eye" sign decreased chronically *(right)*. Vein likewise decreased in circumference. T1 weighted images after gadolinium enhancement *(both right and left)*.

Table II. MRI data for DVT patients

	Acute (≤14 days)	*Chronic (>14 days)*	*p*
All studies	2.38 ± 0.17 (n =31)	1.29 ± 0.44 (n = 8)	$p = 0.001$
All studies (excluding rethrombosed patient)	2.34 ± 0.18 (n = 29)	0.85 ± 0.11 (n = 7)	$p < 0.001$
Paired analysis	2.33 ± 0.20 (n = 8)	1.29 ± 0.44 (n = 8)	$p = 0.03$
Paired analysis (excluding rethrombosed patient)	2.25 ± 0.21 (n = 7)	0.85 ± 0.11 (n = 7)	$p < 0.001$

time. The data were nonlinear, which allowed the determination of a critical timepoint that clearly differentiates the data. Excluding the one patient who had clinical recurrent thrombosis, there was a breakpoint 14 days after the diagnosis that approached statistical significance (n = 38; $p = 0.06$; Fig. 4).

DISCUSSION

Duplex ultrasound has become the preferred diagnostic test for DVT of the lower extremities. This method has limitations, however, particularly in distinguishing chronic from acute clot. In this preliminary study of 14 patients with DVT, we have demonstrated a method for using MRV with gadolinium enhancement to identify acute iliac vein thromboses and to distinguish acute iliac vein thrombus from chronic thrombus. Acute thrombosis in the iliac vein is accompanied by gadolinium enhancement of the vessel wall, which diminishes with time. A ratio of the measured signal intensity at the rim versus the center of a thrombosed vein appears to be elevated in the acute setting, and declines toward or below unity with time. This happens approximately 2 weeks (14 days) after DVT diagnosis.

MRI diagnosis of DVT has been demonstrated previously. Tavares et al.[7] in 1989 described the use of magnetic resonance to detect intraluminal clot. They studied 66 vessels in 45 patients and documented the ability to identify intraluminal clot. They reported a sensitivity and specificity of 85% and 90%, respectively, with combined phase and magnitude spin echo images. Evans et al.[8] reported the results of a prospective comparison study between magnetic resonance and venography in the diagnosis of acute DVT. Using both methods, they imaged 61 consecutive patients suspected of having acute venous thrombosis. They found thrombi in 21 of these patients. They reported a sensitivity and specificity of 100% and 95%, respectively, in the pelvis, 100% and 100%, respectively, in the thigh, and 87% and 97%, respectively, in the calf. Spritzer and colleagues[9] also have reported on the use of MRI in the diagnosis of acute DVT. They reviewed a prospectively collected clinical experience of 199 patients who underwent

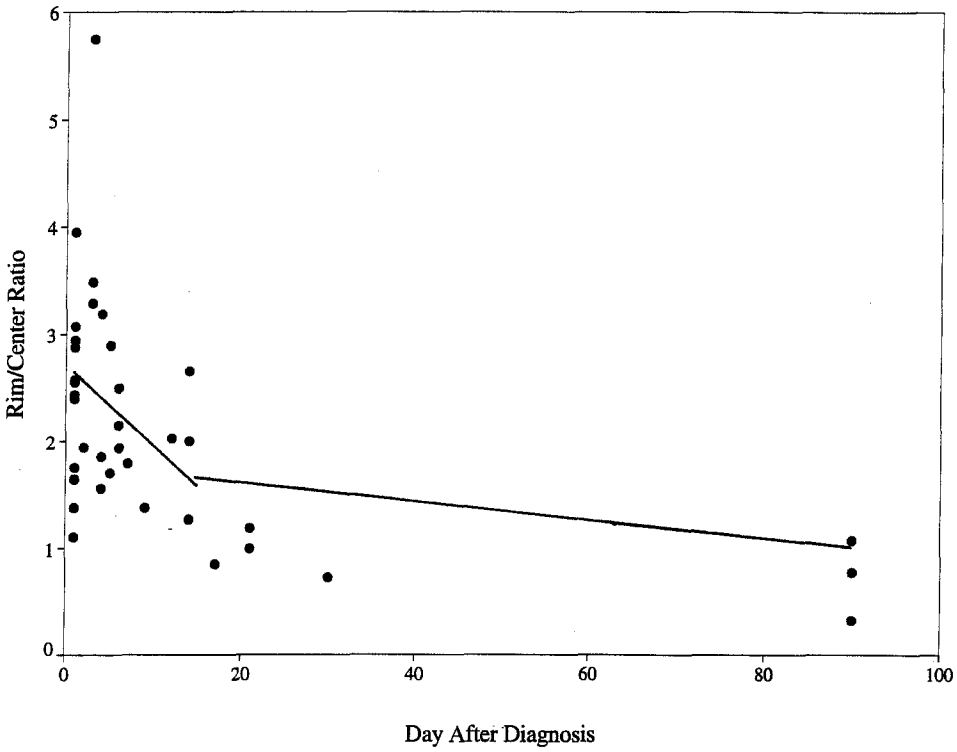

Fig. 4. Piecewise linear regression analysis with best-fit lines for thrombosed veins over time.

gradient recalled echo MRI looking for acute DVT. Of these cases, 79 underwent confirmatory venography, ultrasound, or computed tomography. The sensitivity and specificity were 97% and 95%, respectively. Finally, Carpenter et al.[10] reported a comparison study of 85 patients who underwent MRI, venography, and duplex ultrasound scanning of the infrarenal venous system. The found a sensitivity and specificity for MRI of 100% and 96%, respectively.

Few studies that used MRV have focused on the issue of characterizing the thrombus age. In one such study, Soler et al.[11] reported the use of MRI in inferior vena cava thrombosis. They reported the results of 30 MRI examinations in 17 patients in whom inferior vena cava thrombosis was suspected. Nineteen thrombosed veins were reported, and the patients were divided on the basis of the time from onset of symptoms. The thrombi were then characterized on the basis of homogeneity of signal intensity within the lumen on T1-weighted spin-echo images. Thrombi were classified as either homogeneous or heterogeneous. Classification of image character was done by two independent observers who were blinded to the clinical situation. Six of seven acute thrombi were classified as homogeneous (86%), and nine of 12 nonacute thrombi were classified as heterogeneous (75%; $p < 0.01$).

The use of gadolinium as an intravenous contrast agent has been reported for the MRI evaluation of both arterial and venous structures. Kaufman et al.[12] reported the use of gadolinium-enhanced time-of-flight three-dimensional reconstructions for the evaluation of the vena cava and its branches. Revel and colleagues[13] also described the use of gadolinium as an intravenous contrast agent for the imaging of the vascular anatomy, specifically that in the thorax. Gadolinium chelates decrease the T1 relaxation time, which results in enhancement. Gadolinium extravasates in areas of capillary leak that are related to inflammation and will not simply enhance the areas of edema.[14] This property of gadolinium was used in the present study.

Several studies have documented the ability of gadolinium to selectively increase enhancement on MRI at sites of inflammation. Paajanen et al.[15] used an animal model of inflammation to document focally increased enhancement on MRI after gadolinium infusion. Subcutaneous injection of carrageenan in rats caused local inflammation and enhancement after gadolinium infusion. They also demonstrated

enhancement after gadolinium injection on MRI surrounding liver abscesses. This enhancement, seen at the abscess rim, correlated histologically with the presence of inflammatory cells.[16] Palmer et al.[17] described the use of gadolinium-enhanced MRI of the wrist in human beings to document and quantify joint inflammation. Using gadolinium-enhanced MRI and fluorodeoxyglucose positron emission tomographic scanning of the wrist in 12 patients with arthritic joint inflammation, they demonstrated that enhancement on MRI after gadolinium infusion correlated with fluorodeoxyglucose uptake on positron emission tomographic scans, and that both of these markers of inflammation were strongly associated with clinical findings of active inflammation in the wrists. Others had previously described the use of MRI with gadolinium to visualize synovial inflammation in rheumatoid arthritis.[18,19] Chan et al.[20] reported the use of gadolinium-enhanced MRI in a chinchilla model of otitis media. They used histamine on chinchilla middle ear mucosa and compared gadolinium enhancement with control animals that were pretreated with hydroxyzine (an H1 antagonist), another control group that was pretreated with ranitidine (an H2 antagonist), and a third control group that received both agents. They documented an increase in gadolinium enhancement after the application of histamine and an attenuation of this enhancement in the setting of antihistamines, particularly H1 antagonists. More recently, Ostergaard et al.[21] reported the use of gadolinium-enhanced MRI in 18 arthritic knees before, during, and after intraarticular steroid therapy. Enhancement of the synovial membrane was documented on gadolinium-enhanced T1 weighted magnetic resonance scans before treatment. This enhancement decreased in all the joints imaged within a week of steroid injection. Clinical relapse correlated with a resurgence of synovial enhancement.

Our interest in this study focused on the importance of gadolinium enhancement in the wall and perivenous tissue surrounding a thrombosed vein. This phenomenon was observed initially in animal studies in both a rat model and a primate model of venous thrombosis and was used to evaluate the efficacy of inflammatory inhibition.[22] In those studies, gadolinium-enhanced MRIs were compared with pathologic specimens taken at various time points after thrombus induction by inferior vena cava occlusion.[23] Inflammatory changes seen pathologically corresponded with both the appearance and location of enhancement on MRIs. This inflammatory response in the vein wall and perivenous tissue appears to be mediated by proinflammatory cytokines and adhesion molecules and may serve as a marker of thrombus age. In addition, gadolinium enhancement corresponded to the location of adherent thrombus to the vein wall. In the present study, we did find that gadolinium enhancement does occur in human DVT as it does in animal models. The measurement of a rim-center enhancement ratio allowed for a determination of acute from chronic thrombosis.

This study has several limitations. First, it is small and is intended as a preliminary observation only. Larger numbers of patients will be needed to confirm these findings. A validation study will be needed to determine clinical utility. Second, we evaluated only patients who had iliofemoral venous thrombi. No comment on generalizability can be made until other segments are studied.

CONCLUSION

MRI after gadolinium infusion demonstrates vein wall and perivenous enhanced signal intensity in the setting of acute venous thrombosis. This enhancement results in a characteristic appearance of the thrombosed vein with the rim brighter than the center, the so-called "bull's-eye" sign. Gadolinium enhancement fades with time, which presumably reflects organization of the thrombus and a decrease in inflammation (capillary leak). This finding may aid in the clinical distinction of acute venous thrombosis from chronic venous thrombus. Gadolinium enhancement, as a marker of perivenous inflammation, may therefore also provide a method for the assessment of the inflammatory response to acute venous thrombosis in different settings and assessment of the response to antiinflammatory and antithrombotic treatment for acute DVT.

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