Posttraumatic edema of the lower extremities: Evaluation of the lymphatic vessels with magnetic resonance lymphangiography

Christian Lohrmann, MD,[a] Gregor Pache, MD,[a] Gunter Felmerer, MD,[b] Etelka Foeldi, MD,[c] Oliver Schaefer, MD,[a] and **Mathias Langer, MD,[a]** *Freiburg and Hinterzarten, Germany*

Objective: **To assess for the first time the morphology of the lymphatic system in patients with posttraumatic edema of the lower extremities by magnetic resonance (MR) imaging using the interstitial lymphangiography technique**
Materials and Methods: **Six patients with posttraumatic edema in eight of their 12 lower extremities were examined by MR lymphangiography. Eighteen mL of gadoteridol and one mL of mepivacainhydrochloride 1% were subdivided into 10 portions and injected intracutaneously. MR imaging was performed with a 1.5-T system equipped with high-performance gradients. For MR lymphangiography, a 3D-spoiled gradient-echo sequence was used.**
Results: **In five of the eight (63%) traumatized lower extremities, enlarged lymphatic vessels were detected, with the largest diameter measuring 5 mm. Additionally, a fast lymphatic outflow was observed in seven of the eight (88%) traumatized legs with enhancement of the inguinal lymph nodes already in the first image acquisition 15 minutes after contrast material injection. In two of the eight (25%) traumatized lower extremities, an extensive network of collateral lymphatic vessels was detected at the level of the calf. In both extremities, lymphatic collateralization involved not only the epifascial but also the subfascial lymphatic system. In one patient, who sustained a trauma of the left lower leg with tibial fracture, a small aneurysmatic widening of 7 mm could be detected at the middle level of the calf.**
Conclusion: **MR lymphangiography is a safe and accurate minimal-invasive imaging modality for the evaluation of the lymphatic circulation in patients with posttraumatic edema of the lower extremities. If the extent of lymphatic damage is unclear at the initial clinical examination or requires a better definition for optimal therapeutic planning, MR lymphangiography is able to identify the anatomic and physiological derangements and to establish an objective baseline.**
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Mechanical trauma of the soft tissue and skeleton of the lower extremities is often accompanied by permanent edema at the region of the trauma and the parts distal parts to it.[1] According to Szczesny and Olszewski,[1] around 20% to 25% of patients with mechanical trauma of the legs suffer from this complication, and the extent of the edema is dependent upon the type and the extent of the trauma. Treatment of this condition has also been reported to be difficult, long-lasting, and not very successful. The pathomechanism and, especially, factors responsible for its persistence are, to date, not clarified. However, several studies indicate that besides affecting the venous system with thrombotic events, an injury of the lymphatic system with subsequent tissue fluid and lymph stagnation is likely an additional cause for this edema.[2-5]

Up to now, conventional lymphography and lymphoscintigraphy have been the methods of choice to assess the lymphatic system in patients with posttraumatic edema of the lower extremities.[6-15] However, radiation exposure, invasiveness, and potential side effects like pulmonary embolism have limited the clinical applicability of conventional lymphography. Lymphoscintigraphy also has the disadvantage of ionizing radiation and a low spatial and temporal resolution. In contrast, magnetic resonance lymphangiography (MRL) with intracutaneous application of a water-soluble, paramagnetic contrast agent has proven to be a safe and accurate diagnostic imaging method for the delineation of pathologically modified lymphatic pathways with a high resolution.[16-19] The purpose of this study was to assess for the first time the morphology of the lymphatic system in patients with posttraumatic edema of the lower extremities by magnetic resonance imaging using the interstitial lymphangiography technique.

From the Department of Radiology,[a] and the Department of Plastic and Hand Surgery,[b] University Hospital of Freiburg, and the Foeldi Clinic for Lymphology.[c]

Competition of interest: none.

Reprint requests: Christian Lohrmann, MD, Department of Radiology, University Hospital of Freiburg, Hugstetter Strasse 55, 79106 Freiburg, Germany (e-mail: christian.lohrmann@uniklinik-freiburg.de).

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MATERIALS AND METHODS

Patients. Between April 2006 and April 2007, six patients (age 35-75 years; mean age, 48 years; two female, four male) with clinically proven edema in eight of their 12 lower extremities were referred for MRL and entered into this study (Table I). The study had been approved by our institutional review board, and informed consent had been obtained from all patients prior to MR imaging. The edema of the traumatized legs was unilateral in four patients and bilateral in two patients. The development of the edema in four patients (two with unilateral edema and two with bilateral edema) was associated with a car accident with direct trauma to the lower extremities, pelvic region, and

Table I. Magnetic resonance lymphangiography examinations

MRL examinations	*Number*
Total number of examined patients	6
Patients with unilateral posttraumatic edema	4
Patients with bilateral posttraumatic edema	2
Total number of examined lower extremities	12
Examined lower extremities with posttraumatic edema	8
Examined lower extremities without posttraumatic edema	4

lumbo-sacral region. Unilateral edema in one patient developed after forcible trauma with a metal bar in the area of the right groin while one patient with a lower leg amputation due to a bomb explosion in World War II developed edema in the stump of the remaining upper leg. All patients noticed swelling of the traumatized legs within weeks of the trauma, which gradually increased over time. The time interval between the injury and the MRL varied for five patients between nine months and six years three months (mean, two years eight months). For the injured patient in World War II, the time interval between the trauma and the MRL was about 65 years.

To our knowledge, there was no history of infection or deep vein thrombosis in any of the patients before or after the trauma and none of the patients were treated with anticoagulants on a regular basis. Additionally, at the time of MRL performance, five of the six patients underwent colorflow duplex scanning demonstrating no signs of thrombotic events. Siimilarly, pain, redness, and elevated skin temperature were absent at the time of MRL scanning, excluding complex regional pain syndrome.

After MRL, four patients received conservative treatment with intensive complex decongestive therapy as inpatients. Two patients underwent microsurgical procedures: a lymphatic vessel transplantation in the patient who sustained a forcible trauma with a metal bar in the area of the right groin and a lympho-venous anastomosis at the level of the lower leg in a patient with extensive soft tissue injury. These two patients were also advised to complete their treatment after hospital release with complex decongestive therapy three times per week in an ambulatory setting.

Contrast media. In each patient, a total amount of 18 mL contrast material (Gadoteridol, Prohance, Bracco-Byk Gulden, Konstanz, Germany) and 2 mL mepivacainhydrochloride 1% were subdivided into 10 portions and injected into the dorsal aspect of each foot in the region of the four interdigital webs and medial to the first proximal phalanx. In the patient with the amputated left lower leg, four contrast media depots were placed in the area of the stump. Gadoteridol is a non-ionic, extracellular, micromolecular, water-soluble contrast material for magnetic resonance imaging. It has paramagnetic properties with a gadolinium (Gd) concentration of 0.5 M. Gadoteridol is usually applied intravenously and cleared from the body by glomerular filtration. However, in prior studies, Gadoteridol has been shown to be safe and feasible for MRL after intracutaneous injection without any adverse effects or signs of cutaneous or systemic fibrosis.[16-19]

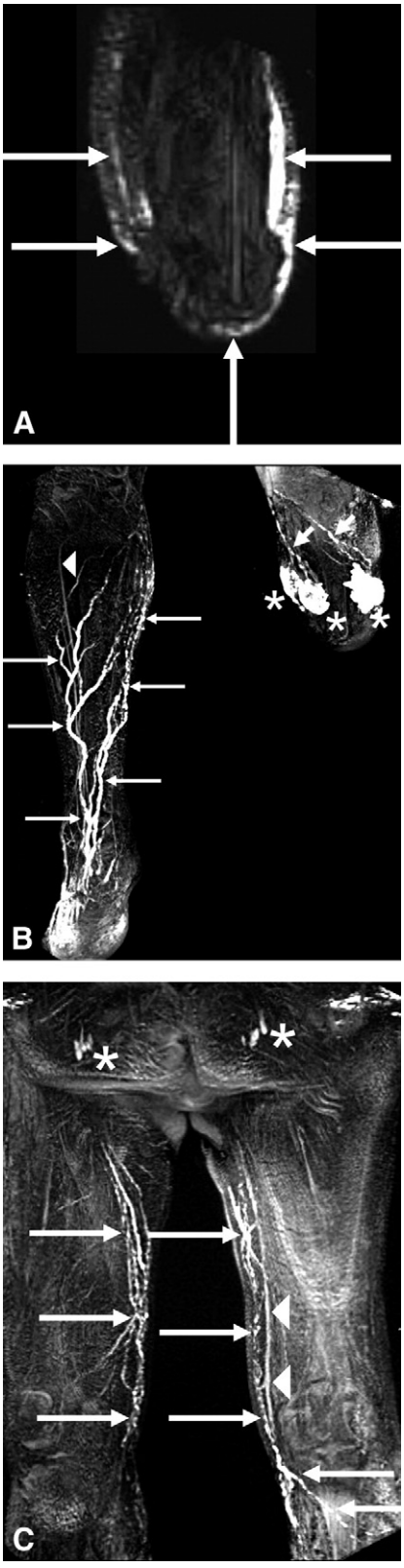
MR imaging examinations. MRL was conducted with a 1.5-T system (Avanto; Siemens Medical Systems, Erlangen, Germany) and three locations were examined: first, the lower leg and foot region; second, the upper leg and the knee region; and third, the pelvic region and the proximal upper leg. The imaging protocol consisted of a heavily T2-weighted 3D-TSE MRI sequence (TR/TE: 2000/694; flip angle: 180°; matrix: 256 × 256, bandwidth: 247 Hz/pixel; 6/8 rectangular field of view 480 mm; slices: 96; voxel size: 2.0 × 1.9 × 1.7 mm; acquisition time: 4 min 48 sec) to evaluate the extent and distribution of the edema. For MRL, a 3D spoiled gradient-echo sequence (Volumetric Interpolated Breathold Examination, VIBE) was performed (TR/TE: 3.58/1.47; flip angle: 35°; matrix: 448 × 448, bandwidth: 490 Hz/pixel; 6/8 rectangular field of view with a maximum dimension of 500 mm; slices: 128; voxel size: 1.2 × 1.1 × 1.2 mm; acquisition time: 1 min 40 sec). To improve vessel-to-background contrast and to facilitate fast and easy interpretability of data, unenhanced 'mask' scans were subtracted from contrast-enhanced datasets (image subtraction).[20-23]

Image analysis. The enhancement of gadoderitol in the lymphatic pathways, inguinal lymph nodes and veins was assessed by two authors. Lymphatic vessels were identified and differentiated from veins based on their beaded appearance. The lymphatic vessels were also evaluated for size and collaterals and their diameter measured. An area of progressive dispersion of the contrast media into the soft tissues was regarded as dermal back-flow. A diagnosis was reached by consensus.

RESULTS

The edema of the traumatized legs, detected by the 3D-TSE MRI sequence, was unilateral in four patients and bilateral in two patients, hence detected in eight of the examined 12 lower extremities. In seven of the lower extremities, the edema demonstrated an epifascial distribution (Fig 1A), while in one lower extremity, an epifascial as well as subfascial component could be detected.

In five of the eight (63%) traumatized lower extremities, the VIBE-sequence revealed lymphatic vessels with a diameter between 3 mm and 5 mm (Table II, Fig 1B, 2A, 2B) while in three of the eight (37%) traumatized lower extremities, the lymphatic vessels diameter ranged between 1 mm and 3 mm (Table II, Fig 2C). Additionally, the dilatation of the lymphatic vessels presented as a diffuse condition, essentially below and at the level of trauma. Furthermore, a fast lymphatic outflow was observed in seven of the eight (88%) traumatized legs with enhancement of the inguinal lymph nodes in the first image acquisition 15 minutes after contrast material injection (Table II). Accompanying venous enhancement was re-



vealed in the lower and upper leg of all 12 examined lower extremities (Fig 1B).

In two of the eight (25%) traumatized lower extremities with severe soft tissue injury, an extensive network of collateral lymphatic vessels was detected at the level of the calf (Table II, Fig 2A, 2B). In both extremities, lymphatic collateralization involved not only the epifascial but also the subfascial lymphatic system (Fig 2C). Furthermore, lymph flow obstruction due to damaged epifascial lymphatic vessels was demonstrated in one lower extremity, resulting in deteriorated lymphatic outflow and delayed enhancement of the inguinal lymph nodes in the 35-minute acquisition post-contrast media injection. Interestingly, the enhancement of the inguinal lymph nodes in the second extremity with an extensive network of collateral lymphatic vessels (patient with bilateral edema) was not delayed and was detected in the first 15-minute acquisition post-contrast media injection, potentially due to the lymphatic outflow compensation of the deep lymphatic system.

In one patient, who sustained a trauma of the left lower leg with tibial fracture, a small aneurysmal widening of a lymphatic vessel up to a diameter of seven mm could be detected at the middle level of the calf (Fig 3). Furthermore, the lateral aspect of the lymphatic system was enhanced in addition to the ventro-medial bundle in this patient. In contrast, in one patient with direct trauma to the upper legs, pelvic and lumbo-sacral region with cutaneous and subcutaneous soft tissue injuries but without pelvic fracture MRL revealed a bilateral epifascial edema with fast lymphatic outflow, resulting in an enhancement of the inguinal lymph nodes 15 minutes after contrast material injection. The diameter of the lymphatic vessels measured up to 2 mm at the level of the lower legs in this patient but no lymphatic collateralisation was noted.

Finally, MRL examinations in the three lower extremities without edema demonstrated a normal lymphatic outflow without manifestations of lymph flow obstruction,

Fig 1. A 75-year-old man with amputed left lower leg due to a bomb explosion in World War II with consecutive development of a lymphedema in the stump of the remaining upper leg. **A,** Coronal heavily T2-weighted 3D-TSE source image demonstrates epifascial lymphedema of the stump (arrows). **B,** Frontal 3D spoiled gradient-echo magnetic resonance lymphangiography (MRL) MIP-image, obtained 25 minutes after gadoteridol injection, clearly depicts several enlarged lymphatic vessels up to a diameter of 3 mm (small arrows) at the lever of the left stump originating from the contrast media injection depots (aterisks). Additionally, several enlarged lymphatic vessels are detected at the level of the clinically inconspicuous right lower leg (large arrows). Note the parallel enhancing vein, which shows a lower signal intensity (arrowhead). **C,** Angled spoiled gradient-echo MRL MIP-image, obtained 25 minutes after gadoteridol injection, reveals several enlarged lymphatic vessels up to a diameter of 3 mm at the level of both knees and upper legs (arrows). Note the parallel enhancing vein at the level of the left upper leg, which shows a lower signal intensity (arrowhead). Early enhanced lymph nodes are demarcated at the level of both inguinal regions (asterisks).

Table II. Magnetic resonance lymphangiography findings in eight examined lower extremities with posttraumatic edema

MRL findings	*Number of extremities*
Lymphatic vessel diameter of 1 mm - 3 mm	3 (37%)
Lymphatic vessel diameter of 3 mm - 5 mm	5 (63%)
Fast lymphatic outflow (enhancement of inguinal LN 15 min post injection)	7 (88%)
Delayed lymphatic outflow (enhancement of inguinal LN 35 minutes post injection)	1 (13%)
Concomitant venous enhancement	8 (100%)
Collateral vessels indicating lymphatic outflow obstruction	2 (25%)

LN, lymph node.

whereby lymphatic vessel diameters ranged between 1 mm and 2 mm. Interestingly, the clinically inconspicuous right lower extremity of the 75-year old man with the amputated left lower leg showed an unclear enlargement of lymphatic vessels up to a diameter of 4 mm (Fig 2A).

DISCUSSION

Etiological classification differentiates between primary (idiopathic) and secondary lymphedema, so that the posttraumatic lymphedema in the patients presented here can be regarded as secondary lymphedema.[24] Regardless, in both types of lymphedema, lymphostasis leads to a development of high protein edema, accumulation of immune cells, fibrosclerosis, and deposition of fat. If adequate treatment is not undertaken, the patient will finally develop lymphostatic elephantiasis and become disabled.[24]

Up to now, conventional lymphography and lymphoscintigraphy have been the primary imaging tools in evaluating the degree of lymphatic damage in patients with

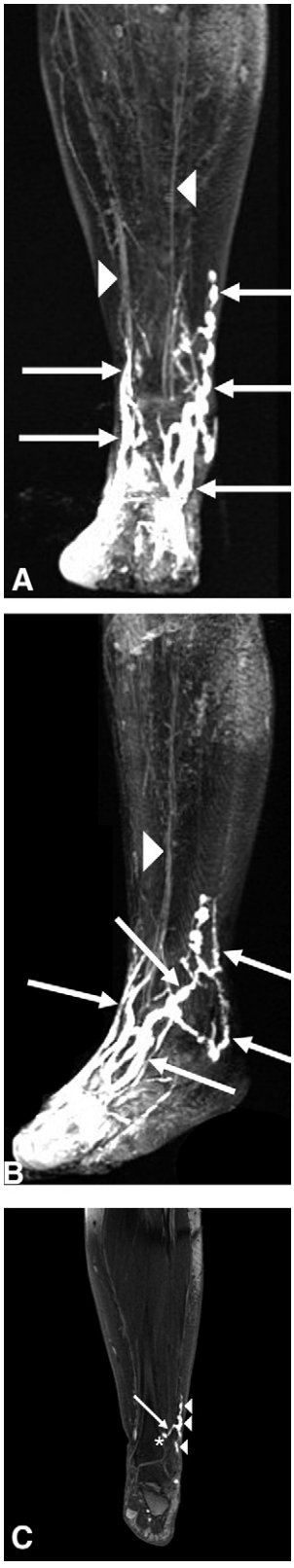


Fig 2. A 40-year-old woman with unilateral secondary lymphedema of the left lower leg due to direct trauma in a car accident. **A,** Frontal 3D spoiled gradient-echo magnetic resonance lymphangiography (MRL) MIP-image, obtained 35 minutes after gadoteridol injection, clearly depicts several enlarged lymphatic vessels at the level of the left foot and lower leg with a network of collateral formations (arrows). Note the parallel enhancing veins, which show a lower signal intensity (arrowheads). **B,** Angled 3D spoiled gradient-echo MRL MIP-image, obtained 35 minutes after gadoteridol injection, clearly depicts seveleral enlarged lymphatic vessels at the level of the left foot and lower leg with a network of collateral formations (arrows). The collateralization involves hereby both the epifascial and subfascial lymphatic system. Note the parallel enhancing vein, which shows a lower signal intensity (arrowhead). **C,** Frontal 3D spoiled gradient-echo source image, obtained 35 minutes after gadoteridol injection, clearly delineates the enlarged epifascial lymphatic vessels (arrowheads), subfascial lymphatic vessels (asterisk), and the perforating lymphatics (arrow), combining the epifascial with the subfascial lymphatic system. Note the close anatomic relationship of the deep lymphatic vessels with the tibia.

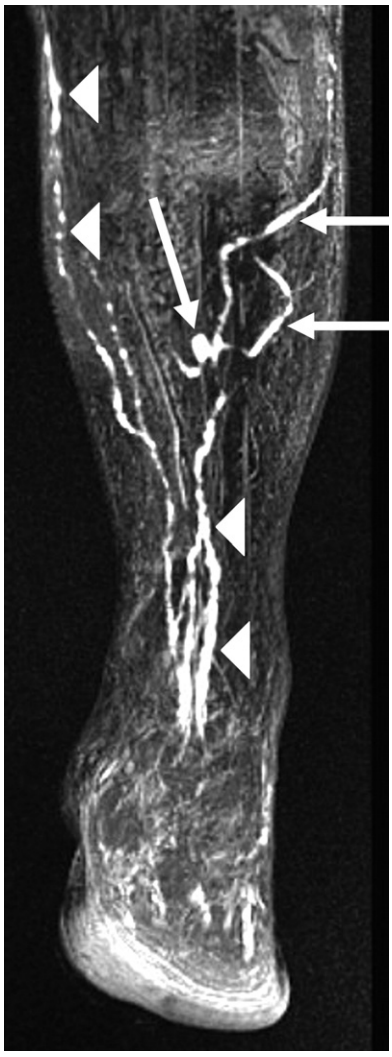


Fig 3. A 35-year-old man with unilateral secondary lymphedema due to a car accident with direct trauma to the left lower leg with tibial fracture. Frontal 3D spoiled gradient-echo magnetic resonance lymphangiography (MRL) MIP-image, obtained 35 minutes after gadoteridol injection, reveals a small lymphatic aneurysm of 7 mm at the middle level of the calf. Furthermore, the lateral aspect of the lymphatic system was enhanced in addition to the ventro-medial bundle.

posttraumatic lymphedema of the lower extremities.[6-15] Conventional lymphography offers the highest concentration of the contrast media in lymphatic vessels and nodes. However, radiation exposure and potential side effects, such as pulmonary embolism, have limited its clinical use. Indeed, some authors are even of the opinion that direct lymphography is obsolete in patients with lymphedema because the oily contrast media damages the lymphatic vessels and worsens the lymphedema.[24]

Lymphoscintigraphy represents the current gold standard in the evaluation of the lymphatic pathways, although it also has the disadvantage of ionizing radiation and provides low spatial and temporal resolution. Despite these disadvantages, many studies have demonstrated lymphoscintigraphy to be a useful method to evaluate functional disturbances of the lymphatic system, using the clearance ratio, and up to now, no alternative imaging modality exists to answer this functional question. Although lymphoscintigraphy has limitations to visualize the lymphatic vessels with a high resolution, it is also possible to demonstrate dermal back-flow areas using this technique indicating lymphatic outflow obstruction and thereby presenting the clinician valuable information for future treatment options.

In contrast, the advantage of MRL, as shown here, is the aquisition of high resolution images of the lymphatic vessels and the lack of radiation. Furthermore, functional information regarding the lymphatic outflow can be achieved, since image acquisitions take place 15, 25, 35, 45, and 55 minutes after contrast material injection. However, the reliability of the functional information obtained from MRL has to be validated in further studies comparing MRL with the gold standard lymphscintigraphy. Regardless, in patients with persistent post-traumatic edema, it appears that MRL can be used to exclude or to confirm a traumatic affection of the lymphatic vessels and to determine the extent of the lymphatic vessel injury (eg, are just the epifascial lymphatic pathways affected or additionally the subfascial system). Other important questions can also be answered (eg, whether a sufficient collateralisation has been established or how dilated the lymphatic vessels are). A major advantage of MRL (compared with lymphoscintigraphy) is also the possibility to precisely visualize and delineate areas of dermal back-flow and the small lymphatic vessels, thereby obtaining the functional information demonstrated by lymphoscintigraphy and describing the number, appearance, and anatomic course of the lymphatic vessels. Finally, with MRL, it is also possible to exactly evaluate and delineate the distribution of the lymphedema using the VIBE- and T2-weighted 3D-TSE sequence, in order to optimize complex decongestive therapy or to select patients suitable for microlymphatic surgery.

Similar to prior MRL studies, accompanying enhancement of veins was seen in all extremities, as Gadoteridol has micromolecular properties and is absorbed by the lymphatic and venous system. However, baseline- and 3D-MIP images at different angles of view helped to identify the lymphatic vessels and differentiate them from veins based on their beaded appearance.[16-19] Foeldi et al reported that lymphatic vessels respond to the lymphatic load in patients with secondary lymphedema in the first stages of the disease with vessel dilatation and a fast lymphatic outflow[24] while in the later stages of the problem, the lymphatic vessels increasingly decompensate with valvular insufficiency, lymph stasis, and delayed lymphatic outflow. At this later stage, MRL findings should demonstrate a single fluid column with no visibility of a beaded appearance of the lymphatics. However, as a fast lymphatic outflow was demonstrated in 88% of the traumatized legs in the current study, this stage of the disease had not been reached by our patients and therefore the use of a "beaded appearance" as

a feature to identify the lymphatic vessels and to differentiate them from veins appeared acceptable.

Several previous studies have strongly linked nephrogenic systemic fibrosis (NSF) to intravenous gadolinium administration for magnetic resonance imaging.[25-27] Additionally, in a recent advisory, the Food and Drug Administration stated that all gadolinium-containing chelates are potentially associated with nephrogenic systemic fibrosis. Most reported cases are linked to gadodiamide (Omniscan) and gadopentetate dimeglumine (Magnevist) and the proposed cause of NSF is release of free Gd^{3+} into tissues in patients with impaired renal function.[28] In contrast, Gadoteridol (Prohance) has a cyclic structure, making it less likely for free Gd^{3+} to be released, and there is only one reported case of NSF associated with gadoteridol use alone.[28] Furthermore, to our knowledge, there is no reported case in the medical literature of local or systemic fibrosis after intracutaneous injection of gadolinium, and prior MRL studies with the intracutaneous injection technique, using gadodiamide and gadoteridol as contrast agents, have not shown any adverse effects or signs of cutaneous or systemic fibrosis. Thus, MRL with intracutaneous injection of Gadoteridol seems to be a safe imaging method for the patient with posttraumatic lymphedema.

Czepelenko et al conducted direct lymphography in 21 patients 1.5 years after open fractures of the lower limb, which were complicated by malunion, protracted wound healing, and scarring of the soft tissues.[6,7] Lymphatic outflow obstruction, dilatation of lymphatic vessels, and lymphatic collateralizations were observed, similar to the results from MRL examinations presented here, which were conducted between nine months and 65 years after injury. Czepelenko et al also demonstrated dermal back-flow areas, which were not observed in our patient series. Several other lymphoscintigraphy studies examining patients after mechanical and operative injuries to the legs, detected increased lymphatic formation and flow[10,11] or enlargement of the regional lymph nodes,[12-14] similar to our findings. Szczesny et al assumed that enlargement of the lymphatic vessels, as was observed in the patients examined with MRL in this study, may be caused by increased lymphatic formation and tissue fluid in the area of the trauma, as well as by paresis of the lymphatic vessel due to locally formed inflammatory substances.[15] In the current study, MRL also demonstrated interruption of the lymphatic vessels in two of the traumatized lower extremities (25%) at the level of the calf with an extensive network of collateral lymphatic vessels. While in one of these two legs the inguinal lymph nodes showed an enhancement 35 minutes after contrast material injection, indicating delayed lymphatic outflow, the inguinal lymph nodes were enhanced already 15 minutes after contrast material injection in the other patient, possibly due to the lymphatic outflow compensation of the deep lymphatic system. This observation describes impressively the capability of the deep lymphatic system to support the lymphatic transport to a certain degree.

Baulieu et al performed lymphoscintigraphy in 32 patients with tibial fractures and found that the alterations of the lymphatic system were significantly more common in the group who developed edema at three months compared with the group without edema.[8] They concluded that early lymphoscintigraphy is a safe test for the prediction of residual edema after tibial fractures. Similarly, Szczesny and Olszewski examined 21 patients with closed lower limb bone fractures and soft tissue injuries with lymphoscintigraphy[9] but found no interruption of calf or thigh lymphatic vessels on lymphoscintigraphies in any of the patients. However, Szczesny and Olszewski detected dilatation of lymphatic vessels in all (100%) examined extremities and a decrease in lymphatic flow rate in these vessels.[9] In the current study, MRL examinations showed enlarged lymphatic vessels in 63% of the traumatized lower extremities, with the largest diameter measuring 5 mm. The dilatation of the lymphatic vessels was also demonstrated to be a diffuse condition, essentially below and at the level of trauma. Interestingly, the clinically inconspicuous right lower extremity of the 75-year old man with amputated left lower leg showed an unclear enlargement of lymphatic vessels up to a diameter of 4 mm.

Szczesny and Olszewski also reported an enlargement of inguinal lymph nodes in 62% of cases and rapid visualization (within 30 minutes) of lymphatic vessels of the injured extremity in eight patients (38%), while in 12 patients (57%), lymphatic vessels were visualized after 45 minutes, simultaneous with the contralateral limb. In two patients, a network of superficial lymphatic vessels was seen, indicating local obstruction. Similarly, in the current study, MRL revealed a fast lymphatic outflow in 88% of the traumatized legs with enhancement of the inguinal lymph nodes in the first image acquisition 15 minutes after contrast material injection. These observations correlate well with the theory by Foeldi et al, that the lymphatic vessels respond to the lymphatic load in patients with secondary lymphedema (eg, posttraumatic lymphedema) in the first stages of the disease with a dilatation and a fast lymphatic outflow.[24] Finally, Szczesny and Olszewski reported that the type of lymphatic system changes were similar, irrespective of whether a fracture or only soft tissue injury existed and whether the injury was complicated or not by thrombosis of the venous system.[9] These observations were confirmed in animal experiments using intravital fluorescence and standardized mechanical injury of hind limbs[29] so that Szczesny and Olszewski concluded, in summary, that both clinical and experimental observations support the theory of an inflammatory process being responsible for the persistent posttraumatic edema of lower extremities.[9]

In conclusion, MRL is a safe and accurate diagnostic imaging method for the evaluation of the lymphatic circulation in patients with posttraumatic edema of the lower extremities. If the extent of lymphatic damage in patients with posttraumatic edema is unclear by clinical examination alone or requires a better definition for optimal therapeutic planning (complex decongestive therapy, microvascular surgery), MRL is an excellent, minimally-invasive imaging modality with a high resolution to identify the anatomic and physiological derangements of the lymphatic system

and to establish an objective baseline. Additionally, due to the minimal-invasiveness and lack of radiation associated with the procedure, diagnostic follow-up MRLs can be performed routinely and with no risk for the patient.

AUTHOR CONTRIBUTIONS

Conception and design: CL, EF, ML
Analysis and interpretation: CL, GP, GF
Data collection: CL, GP, GF, EF
Writing the article: CL, GP
Critical revision of the article: CL, GP, GF, EF, OS, ML
Final approval of the article: CL, OS, ML
Statistical analysis: N/A
Obtaining funding: N/A
Overall responsibility: CL, ML

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