Real-time magnetic resonance imaging of deep venous flow during muscular exercise—preliminary experience

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Background: The accurate assessment of peripheral venous flow is important for the early diagnosis and treatment of disorders such as deep-vein thrombosis (DVT) which is a major cause of post-thrombotic syndrome or even death due to pulmonary embolism. The aim of this work is to quantitatively determine blood flow in deep veins during rest and muscular exercise using a novel real-time magnetic resonance imaging (MRI) method for velocity-encoded phase-contrast (PC) MRI at high spatiotemporal resolution.

Methods: Real-time PC MRI of eight healthy volunteers and one patient was performed at 3 Tesla (Prisma fit, Siemens, Erlangen, Germany) using a flexible 16-channel receive coil (Variety, NORAS, Hoechberg, Germany). Acquisitions were based on a highly undersampled radial FLASH sequence with image reconstruction by regularized nonlinear inversion at 0.5x0.5x6 mm³ spatial resolution and 100 ms temporal resolution. Flow was assessed in two cross-sections of the lower leg at the level of the calf muscle and knee using a protocol of 10 s rest, 20 s flexion and extension of the foot, and 10 s rest. Quantitative analyses included through-plane flow in the right posterior tibial, right peroneal and popliteal vein (PC maps) as well as signal intensity changes due to flow and muscle movements (corresponding magnitude images).

Results: Real-time PC MRI successfully monitored the dynamics of venous flow at high spatiotemporal resolution and clearly demonstrated increased flow in deep veins in response to flexion and extension of the foot. In normal subjects, the maximum velocity (averaged across vessel lumen) during exercise was 9.4±5.7 cm·s⁻¹ for the right peroneal vein, 8.5±4.6 cm·s⁻¹ for the right posterior tibial vein and 17.8±5.8 cm·s⁻¹ for the popliteal vein. The integrated flow volume per exercise (20 s) was 1.9, 1.6 and 50 mL (mean across subjects) for right peroneal, right posterior tibial and popliteal vein, respectively. A patient with DVT presented with peak flow velocities of only about 2 cm·s⁻¹ during exercise and less than 1 cm·s⁻¹ during rest.

Conclusions: Real-time PC MRI emerges as a new tool for quantifying the dynamics of muscle-induced flow in deep veins. The method provides both signal intensity changes and velocity information for the assessment of blood flow and muscle movements. It now warrants extended clinical trials to patients with suspected thrombosis.

Keywords: Deep venous flow; real-time MRI; phase-contrast MRI

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Introduction

Deep-vein thrombosis (DVT) is an important area of research as it is a major cause of post-thrombotic syndrome or even death due to pulmonary embolism (1-3). A diagnosis at an early stage may save lives through focused therapy. Although contrast venography has been considered as the gold standard for the diagnosis of DVT (4), it is invasive and requires contrast media. Presently, duplex and compression ultrasonography is the preferred technique to image flow in the proximal veins of the lower leg (5). It combines morphological (e.g., thrombus) and functional aspects (e.g., venous flow) with a functional stress test such as gentle pressure on the veins (i.e., compression). Further advantages are widespread availability and cost efficacy. However, its applicability to small deep veins is hampered by the presence of bones, muscles and soft tissues which affect the quality of ultrasound signal recording (6,7). Ultrasound measurements are operator dependent and lack standardized protocols for obtaining blood vessel diameter, lumen or quantitative flow measurements, in particular in pathologic anatomies like post-thrombotic syndromes or varicose veins.

Magnetic resonance imaging (MRI) has also been used to measure flow through velocity-encoded phase-contrast (PC) techniques (8-10). The method requires two acquisitions with velocity-compensated and velocity-encoding gradients to assess through-plane flow perpendicular to the imaging section. A subsequent phase difference operation of the two complex images provides a T1-weighted magnitude image of the anatomy and a PC velocity map of moving or flowing signals. Although PC MRI has recently been combined with parallel imaging (11,12) and non-Cartesian acquisition schemes (13,14) to reduce acquisition times, most of these techniques still rely on ECG-gating and the underlying assumption of cardiac periodicity (15) which precludes the application to non-cardiac related flow. In contrast, real-time flow MRI techniques promise flow information of arbitrary dynamic processes (16-18). Unfortunately, these early studies sacrificed spatial resolution to achieve sufficient temporal resolution and therefore were unable to monitor flow in small blood vessels such as the veins of the lower leg. Most recently, real-time MRI using highly undersampled radial FLASH with image reconstruction by regularized nonlinear inversion (NLINV) has been developed to provide images at both high spatial and temporal resolution (19-21). This technique has further been extended to quantitatively image through-plane flow in real time (22-24) and successfully been applied to a number of clinical scenarios (25-27). The aim of this study was to explore the potential of real-time PC MRI to assess deep venous flow at high spatial and temporal resolution in normal subjects.

Methods

Subjects and MRI

Flow MRI was performed at 3 Tesla (Prisma fit, Siemens Healthcare, Erlangen, Germany) with use of a 16-channel receive coil (Variety, NORAS, Hoechberg, Germany). The coil consists of two very flexible 8-channel elements which were easily wrapped around the subjects lower leg. They are specially designed to study smaller objects at excellent signal-to-noise ratio compared to the standard coils of the MRI vendor.

A group of eight healthy volunteers (age 25–62 years) with no known illness and a patient with DVT (total occlusion) in the popliteal vein (confirmed by duplex-ultrasound) were recruited after approval by the institutional review board of the University Medical Center Göttingen. All participants gave written informed consent before MRI. Subjects were studied in supine position with a feet-first position inside the scanner. A protocol of muscular exercise was visually projected to the subjects during real-time MRI. While the protocol for healthy volunteers consisted of an initial rest phase of 10 s, foot flapping of 20 s and another rest phase of 10 s, the patient started with a rest phase of 16 s followed by a foot flapping phase of 24 s to better detect residual flow during compromised muscle performance. During foot flapping, the subjects were asked to perform flexion and extension of the foot in an alternating fashion without specific instructions about the frequency. Flow measurements were performed in two cross-sections of the leg at about the mid-region of the calf muscle and close to the knee. The total examination time per subject in the scanner was about 30 min.

Real-time PC MRI

Real-time PC MRI was performed using highly undersampled radial FLASH with image reconstruction by regularized nonlinear inversion (NLINV) as previously described (24). The scan parameters for the measurement were: in-plane resolution 0.5×0.5 mm², field of view 128×128 mm², matrix size 256×256 pixels, repetition time...
Cardiovasc Diagn Ther shows the mean velocities and corresponding Figure 2C,D, real-time PC MRI provides high-
depicts time courses of the mean velocities of shows the net
summarizes the exercise-induced maximal all subjects and therefore chosen for analysis, while two
positions of the lower leg. These vessels were seen in
popliteal vein, right peroneal vein, and popliteal vein at two different
allow for a proper delineation of the right posterior tibial
As shown in Figure 1, real-time PC MRI provides high-
velocities averaged across the respective vessel lumen and
corrections as any displacement of a vessel is taken care of
Online reconstruction of real-time images was achieved by running a parallelized version of the NLINV algorithm
a bypass computer (sysGen/TYAN Octuple-GPU, Sysgen, Bremen, Germany) equipped with two processors
The velocity sensitivity (VENC) was adjusted to a value between 80 and 95 cm·s⁻¹ to avoid phase wrapping for
the segmentation algorithm. Flow parameters included velocities averaged across the respective vessel lumen and
corresponding flow volumes. In addition, signal intensity
The observation of large variations in this group of healthy
muscular performance. Similarly, Table 2 shows the net volume of upward flow towards the heart in deep veins.
The values represent the integrated response to multiple

### Results

As shown in Figure 1, real-time PC MRI provides high-
resolution magnitude images and PC velocity maps which allow for a proper delineation of the right posterior tibial
vein, right peroneal vein, and popliteal vein at two different positions of the lower leg. These vessels were seen in
all subjects and therefore chosen for analysis, while two
peroneal or posterior tibial veins were detected in only a
few cases. During exercise, the method yields quantitative
information about the performance of the gastrocnemius muscle which influences the venous flow. In PC velocity
maps, venous and arterial flow are represented as white and black signal, respectively, in accordance to their respective
upward and downward direction of flow.

Figure 2 depicts time courses of the mean velocities of the gastrocnemius muscle and peroneal artery as well as of the right peroneal and posterior tibial vein in response to exercise at the level of the calf muscle. It is clearly seen that deep venous flow in the lower leg (Figure 2C,D) almost exclusively occurs during muscle movement, i.e., synchronous to the contraction (forward and backward velocity) of the gastrocnemius muscle during foot flapping. This is accompanied by an increased flow velocity in the peroneal artery.

Table 1 summarizes the exercise-induced maximal velocities in deep veins obtained during foot flapping for all subjects (mean and SD during the exercise phase). These flow velocities across subjects were about 8 to 10 cm·s⁻¹ in the right peroneal and posterior tibial vein and almost twice as high in the popliteal vein, respectively. The observation of large variations in this group of healthy volunteers most likely reflects individual differences in muscular performance. Similarly, Table 2 shows the net volume of upward flow towards the heart in deep veins. The values represent the integrated response to multiple foot flaps during the 20 s period of exercise. Mean values across subjects were only up to 2 mL for the right peroneal and posterior tibial vein, whereas the net flow volume in the popliteal vein of 50 mL (i.e., approximately 4 to 5 mL per foot flap) results from the accumulation of venous return from the lower leg which leads to a larger diameter and higher flow velocity.
Figure 1 Selected real-time T1-weighted images and PC maps of deep venous flow (bright signal in PC maps = upward flow) during muscle movement (subject #5). (Top) At the level of the calf muscle: arrows from left to right refer to the right and left peroneal vein as well as right and left posterior tibial vein, the circle represents the gastrocnemius muscle (see Figures S1,S2). (Bottom) At the level of the knee: popliteal vein (arrow) and gastrocnemius medial head muscle (circle, see Figures S3,S4). PC, phase-contrast.

The results for a patient with DVT are shown in Figures 4 and 5. Although flow in the popliteal artery and saphenous vein are clearly seen in both the magnitude image and PC velocity map (Figure 4), the popliteal vein is poorly identified due to very low flow caused by thrombus blockage in the vessel. During foot flapping, which was only possible for a few seconds as indicated by increased through-plane velocity and signal changes during the initial phase, the popliteal vein revealed no significant increase in blood flow velocity (Figure 5). In contrast, the observation of a moderate increase of flow in the saphenous vein seems to indicate a compensatory mechanism of venous flow in response to thrombosis of the popliteal vein. However, flow in the saphenous vein turned out to be complex and spatially heterogeneous which may affect the quantitative analysis.

Discussion

Real-time PC MRI was successfully applied to dynamically monitor exercise-related changes of blood flow in the deep veins of the lower leg. A spatial resolution of 0.5 mm allowed for a proper delineation and segmentation of small blood vessels. Because muscular activity was employed as the primary driving force for flow in this study, a temporal resolution of 100 ms was fully sufficient to account for respective changes in flow.

Previous studies of the veins of the limbs (30-32) reported a modulation of venous flow by respiration. In contrast, the present findings clearly demonstrate that
flow in the deep veins of the lower leg is very small and mainly driven by arterial pulsation during resting phases with normal breathing, while much higher venous return from the lower limbs to the heart occurs during muscle movements such as foot flapping. This latter observation confirms the results of a respiration-synchronized PC flow MRI study (31), which reported flow velocities of 15 to 19 cm·s\(^{-1}\) in the popliteal vein during mild calf exercise in excellent agreement with the values reported in Table 1. Though the influence of exercise on arterial supply to the lower leg was not in the focus of this work, the data for the peroneal artery suggests that both arterial flow velocity and direction are affected by the strength and direction of muscular movements. In general, flow (i.e., velocity and volume) in the popliteal vein at the lower knee was found to be much higher than in the deep veins at the level of the calf muscle. Flow volumes not only reflect the mean (or integrated) velocity across the vessel lumen, but also the effective size of the lumen during flow. For the present subjects these values differed between calf veins and the popliteal vein by almost a factor of 4. The remaining difference must be ascribed to the facilitated flow in a larger vessel where border zones have less influence. These conditions yield a twofold higher mean velocity (Table 1) and most likely lead to a much more effective laminar (i.e., parabolic) flow profile across the lumen.

Movements of the muscles involved in foot flapping were not analyzed in detail, although the velocities of the

Figure 2 Mean velocities of gastrocnemius muscle, peroneal artery, right peroneal vein, and right posterior tibial vein at the level of the calf muscle (subject #5) for 10 s of rest, 20 s foot flapping, and 10 s rest at 100 ms resolution.

Figure 3 (Top) mean velocities and (Bottom) signal intensities of gastrocnemius medial head muscle and popliteal vein at the level of the knee (subject #2) for 10 s of rest, 20 s foot flapping, and 10 s rest at 100 ms resolution.
Table 1 Mean maximal velocities in deep veins during muscle movement

<table>
<thead>
<tr>
<th>Subject</th>
<th>Peroneal vein</th>
<th>Posterior tibial vein</th>
<th>Popliteal vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>6.2±1.8</td>
<td>6.0±2.3</td>
<td>21.8±3.7</td>
</tr>
<tr>
<td>#2</td>
<td>7.8±2.8</td>
<td>7.6±2.0</td>
<td>18.3±6.5</td>
</tr>
<tr>
<td>#3</td>
<td>17.9±6.3</td>
<td>12.1±5.3</td>
<td>19.2±5.3</td>
</tr>
<tr>
<td>#4</td>
<td>8.9±2.5</td>
<td>9.2±4.2</td>
<td>4.8±2.1</td>
</tr>
<tr>
<td>#5</td>
<td>17.2±3.6</td>
<td>17.5±5.2</td>
<td>19.7±7.3</td>
</tr>
<tr>
<td>#6</td>
<td>10.6±10.5</td>
<td>4.4±2.2</td>
<td>17±7.9</td>
</tr>
<tr>
<td>#7</td>
<td>3.2±2.3</td>
<td>3.2±2.3</td>
<td>17.3±6.9</td>
</tr>
<tr>
<td>#8</td>
<td>3.3±1.1</td>
<td>8.0±3.4</td>
<td>24.6±6.2</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>9.4±5.7</td>
<td>8.5±4.6</td>
<td>17.8±5.8</td>
</tr>
</tbody>
</table>

Table 2 Net flow volume in deep veins during muscle movement

<table>
<thead>
<tr>
<th>Subject</th>
<th>Net flow volume/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peroneal vein</td>
</tr>
<tr>
<td>#1</td>
<td>3.2</td>
</tr>
<tr>
<td>#2</td>
<td>0.0</td>
</tr>
<tr>
<td>#3</td>
<td>2.7</td>
</tr>
<tr>
<td>#4</td>
<td>1.4</td>
</tr>
<tr>
<td>#5</td>
<td>6.8</td>
</tr>
<tr>
<td>#6</td>
<td>1.7</td>
</tr>
<tr>
<td>#7</td>
<td>0.0</td>
</tr>
<tr>
<td>#8</td>
<td>−0.7</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.9±2.4</td>
</tr>
</tbody>
</table>

1°, summed response to multiple foot flaps during 20 s of exercise. SD, standard deviation.

Figure 4 Selected real-time T1-weighted image and PC map of deep venous flow of a patient with DVT at the level of the knee. Arrows refer to (left) saphenous vein and (right) popliteal vein, the circle represents the gastrocnemius medial head muscle. PC, phase-contrast; DVT, deep-vein thrombosis.

gastrocnemius muscle for all subjects were in the range of 10 to −10 cm·s$^{-1}$ for flexion and extension. In future studies it may be considered to directly correlate venous flow and muscular involvement in the lower leg.

While quantitative flow studies are best accomplished by analyzing PC velocity maps, signal intensities in corresponding magnitude images provide qualitative diagnostic information of enhanced sensitivity as exploited in a real-time MRI study of cerebrospinal fluid flow (26). Such complementary data without the need for another measurement may turn out to be useful for studies of patients with DVT who are either unable to perform suitable muscle movements or suffer from severe thrombosis with little or no venous flow. In fact, this situation holds true for a DVT patient where the intensities in the popliteal vein in response to exercise offered a better contrast-to-noise ratio for the assessment of residual flow than the corresponding velocities.
As this work represents a pilot study of blood flow in peripheral veins, it has limitations due to a small sample size and the lack of reproducibility tests. On the other hand, the actual real-time MRI method and its extension to PC flow imaging have extensively been validated in previous publications dealing with the actual technology, experimental flow phantoms, and aortic blood flow in healthy subjects (21-24). Another potential confound arises from interindividual differences in muscular performance with respect to amplitude, speed and frequency of foot flapping. Although a direct correlation with the actual muscular involvement might be possible by using the simultaneous velocity information for specific muscle groups, this was beyond the scope of this proof-of-concept study. Finally, residual streaking artifacts in PC velocity maps may appear around high-flow arteries and eventually affect the phase information in neighboring veins. While no major complication was observed in the present study, the problem may be resolved by a more advanced reconstruction technique for real-time PC flow MRI which almost completely avoids such artifacts (33).

In conclusion, real-time PC MRI offers a fast and robust tool for simultaneously measuring cardiac-driven arterial flow and muscle-induced flow in all peripheral veins. The approach may become of clinical value in a variety of disorders such as varicose veins, post-thrombotic syndrome and DVT as the major cause of life-threatening pulmonary thromboembolism. Although ultrasound of blood flow in proximal veins such as the saphenous vein is the current standard for examination of thrombosis in the lower leg, MRI may be beneficial in cases of ultrasound failure (e.g., difficult DVT locations) or in the quantitative assessment of reflow after successful recanalization by pharmacologic or mechanic thrombolysis. Real-time PC MRI of deep veins therefore awaits clinical trials of larger cohorts of patients to ascertain its sensitivity and specificity for the assessment of compromised venous return.

Acknowledgements

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Footnote

Conflicts of Interest: J Frahm is co-inventor of a patent...
covering the real-time MRI technique used in this study. The other authors have no conflicts of interest to declare.

Ethical Statement: All participants were recruited after ethics approval by the institutional review board of the University Medical Center Göttingen (approval number: 11/9/11). All participants gave written informed consent before MRI.

References


Figure S1 Real-time MRI movie of T1-weighted images of a healthy subject (calf muscle) during 10 s rest, 20 s foot flapping, and 10 s rest (400 frames at 10 fps) (34). MRI, magnetic resonance imaging. Available online: http://www.asvide.com/articles/1298

Figure S2 Real-time MRI movie of PC maps of a healthy subject (calf muscle) corresponding to Figure S1 (35). MRI, magnetic resonance imaging; PC, phase-contrast. Available online: http://www.asvide.com/articles/1299

Figure S3 Real-time MRI movie of T1-weighted images of a healthy subject (knee) as in Figure S1 (36). MRI, magnetic resonance imaging. Available online: http://www.asvide.com/articles/1300

Figure S4 Real-time MRI movie of PC maps of a healthy subject (knee) corresponding to Figure S3 (37). MRI, magnetic resonance imaging; PC, phase-contrast. Available online: http://www.asvide.com/articles/1301

Figure S5 Real-time MRI movie of T1-weighted images of a patient with DVT (knee) during 16 s rest followed by foot flapping (400 frames at 10 fps) (38). MRI, magnetic resonance imaging; DVT, deep-vein thrombosis. Available online: http://www.asvide.com/articles/1302

Figure S6 Real-time MRI movie of PC maps of patient with DVT (knee) corresponding to Figure S5 (39). MRI, magnetic resonance imaging; PC, phase-contrast; DVT, deep-vein thrombosis. Available online: http://www.asvide.com/articles/1303
References


