Peripheral Nerve Perfusion by Dynamic Contrast-Enhanced Magnetic Resonance Imaging

Demonstration of Feasibility

Philipp Bäumer, MD, MSc,* Maximilian Reimann, * Clemens Decker, PhD, † Alexander Radbruch, MD, JD,* Martin Bendzus, MD,* Sabine Heiland, PhD, † and Mirko Pham, MD*

Purpose: The aim of this study was to establish dynamic contrast-enhanced perfusion in peripheral nerves for determination of blood-nerve permeability (Ktrans) and nerve blood volume (NBV) in peripheral neuropathies as compared with healthy controls.

Methods: The study was approved by the institutional ethics committee, and written informed consent was obtained from all participants. Forty-three controls (24 women, 19 men; age, 48.7 ± 17.5 years) and 59 patients with peripheral neuropathy (28 women, 31 men; age, 52.7 ± 12.4 years) were examined by a standard protocol including a T1-weighted dynamic contrast-enhanced sequence (time of repetition/time of echo, 4.91/1.64; 10 slices; resolution 0.8 × 0.6 × 3.0 mm3). Time - signal intensity analysis was performed by normalizing to pre-bolus arrival and calculating the mean contrast uptake (MCU) for each patient. Further analyses were performed by customized software to calculate Ktrans and NBV. Statistical analysis included 2-sided Student’s t tests of controls versus patients, receiver operating characteristic analysis, and subgroup analysis of patients according to etiologies of neuropathy.

Results: Time-signal intensity analysis showed significantly increased contrast uptake in patients as compared with controls (MCU, 1.29 ± 0.15 vs 1.18 ± 0.08; P < 0.001). This was caused mainly by an increase in Ktrans (0.046 ± 0.025 vs 0.026 ± 0.016 min⁻¹; P < 0.001) and less by an increase in NBV (3.9 ± 2.6 vs 3.0 ± 1.9 ml/100 ml; P = 0.12). This trend was true for all etiologies except entrapment neuropathies. Excluding these, receiver operating characteristic analysis found an area under the curve of 0.78 (95% confidence interval, 0.69–0.89) for MCU and 0.77 (95% confidence interval, 0.65–0.90) for Ktrans to discriminate neuropathy from control.

Conclusions: Dynamic contrast-enhanced perfusion is a feasible technique to assess Ktrans and NBV in peripheral nerves and may be used in future investigations on peripheral neuropathies.

Key Words: peripheral nerves, MR Neurography, MRI, perfusion, permeability

Received for publication November 26, 2013; and accepted for publication, after revision January 22, 2014.

From the *Department of Neuroradiology and †Section of Experimental Radiology, Department of Neuroradiology, Heidelberg University Hospital, Heidelberg, Germany.

Conflicts of interest and sources of funding: This study was supported by a Postdoctoral-Fellowship grant to PB, from the Medical Faculty of the University of Heidelberg, M.P. is supported by the EFSJ/DJRF/Novo Nordisk European Programme in Type 1 Diabetes Research.

Reprints: Philipp Bäumer, MD, MSc, Department of Neuroradiology, Heidelberg University Hospital, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany. E-mail: philipp.baumer@med.uni-heidelberg.de.

Copyright © 2014 by Lippincott Williams & Wilkins. ISSN: 0020-9996/14/4908-0518

www.investigativeradiology.com

518 | Investigative Radiology • Volume 49, Number 8, August 2014

Copyright © 2014 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
MRN Imaging
Examinations were conducted at 3 T magnetic field strength (Magnetom VERIO; Siemens AG, Erlangen, Germany) between January and July 2013. First, a T1-weighted turbo-spin-echo sequence with spectral fat saturation and at high spatial resolution for reliable recognition and segmentation of peripheral nerves was acquired. The slab position of this first sequence was chosen based on the patient’s known or most likely localization of maximum nerve lesion as suspected by clinical and electrophysiological findings. At this position, a T1-weighted DCE volume interpolated breath examination sequence was acquired for the detection of contrast uptake and further quantitative analysis. A contrast agent (DOTAREM; Guerbet, Villepinte, France) was administered at the beginning of the third frame and 35 frames were recorded at a rate of 6.11 seconds per frame. A T1-weighted sequence with fat saturation after administration of contrast agent was then acquired at the same position in 79 of the 102 subjects. Sequence parameters are given in Table 1.

Quantitative Image Analysis

Time–Signal Intensity Curve Analysis

Using the software mean curve on a Syngo-workstation (Syngo VE 32 B; Siemens), peripheral nerve signal was analyzed for all time points, and time–signal intensity curves were plotted. Since no automated method is established for the registration of peripheral nerves, masks for peripheral nerves were obtained by precise manual segmentation around the epineurial contour (Fig. 1) of all peripheral nerves at all slice positions (median, ulnar, and radial nerves for upper arm examinations; median and ulnar nerves for elbow and wrist; sciatic nerve for thigh; and peroneal and tibial nerve for knee examinations). The most proximal and distal positions (1 and 10) were discarded because of potential 3-dimensional aliasing artifacts at the extremes of the imaging slab. An additional mask was placed in the largest artery contained in the imaging slab to derive the arterial input function (AIF) and to determine the exact time point of bolus arrival in the examined body region. Absolute signal intensity values for each mask were read out and then normalized to the arithmetic mean of the pre–bolus arrival frames (6–8 frames) by division. These values then allowed plotting of an individual time–signal intensity curve for each nerve to calculate 1 single value, denoted as mean contrast uptake (MCU).

Quantitative Analysis Using the Patlak Model

We used the Patlak model to estimate the transfer constant ($K_{trans}$) between intravascular and extravascular space and nerve blood volume (NBV). Although the Patlak model was developed for irreversible tracer uptake, it can also be used in first-order kinetics if the influence of the diffusion of contrast agent from the extravascular back to the intravascular space is negligible, which is a valid assumption when $K_{trans}$ is relatively low and the observation time is short. In this case, $K_{trans}$ and NBV can be determined by linear regression of

$$x = \frac{\int AIF(t) \, dt}{AIF(0)}$$

and

$$y = \frac{c(t)}{AIF(0)},$$

considering the equation

$$y(t) = NBV + K_{trans} \cdot x(t),$$

where AIF(t) is the concentration of contrast agent in the supplying artery at a given time point t and c(t) is the contrast agent concentration measured in tissue.

We used a customized software package developed in our department (O2dicom) to determine $K_{trans}$ (in min$^{-1}$) and NBV (in mL/100 mL) in the peripheral nerve masks. O2dicom is written in JAVA and is based on the Patlak model to calculate $K_{trans}$ and NBV as described above semiautomatically either on a pixel-by-pixel basis or in regions of interest. A linear relationship between measured signal intensity and contrast concentration was assumed. All signal values up to the time point of bolus arrival were used for normalization. Computed analysis in several cases failed to calculate parameters because the subjects’ AIF was insufficient for analysis by the Patlak model. Furthermore, pulsation artifacts by adjacent vessels occasionally impaired quantitative analysis. We therefore set respective upper and lower limits for $K_{trans}$ as 0.1 and 0.0 min$^{-1}$ and NBV as 10 and 0.0 mL/100 mL and excluded all subjects in whom these limits were passed at any slice position.
mean values and box plots for KMCU, Ktrans, Origin Pro 9.0 (Northampton, MA). Mean values were calculated for patients. Graphs mapping the time elapsed between contrast arrival in the arterial system is at time point = 0. Patients with neuropathy show distinctly increased uptake already within 1–2 min while normal nerves fall in the range of control subjects and not in the range of neuropathies of other etiologies. The ROC analysis was performed to assess the potential of perfusion read-out parameters as diagnostic markers for the presence of peripheral neuropathy. Whereas NBV was found to be a weak marker, MCU and Ktrans provided considerable diagnostic accuracy for the detection of peripheral neuropathy (ROC values are given in Fig. 5). Since values in entrapment neuropathies fell in the range of controls and not in that of neuropathies of other etiologies, their exclusion yielded improved diagnostic accuracy (Table 3).

Perfusion parameter values were independent of the body region in which they were assessed in healthy controls; for example, no statistically significant differences were found between proximal versus distal locations or between upper and lower extremities. Because

RESULTS

A total of 102 participants participated in the study: 43 were included as control subjects and 59 subjects were included as patients based on clinical and electrophysiological results. Patients were further classified by etiology into 12 patients with an entrapment neuropathy, 22 patients with an inflammatory neuropathy, 4 patients with traumatic nerve injury, 2 patients with a known hereditary polyneuropathy, and 19 patients with a polyneuropathy of yet undetermined cause. Neuropathies caused by tumors of the PNS were excluded from the study. By body region, examinations covered the upper arm in 12 controls and 21 patients, respectively, the elbow in 10 and 14, the wrist in 5 and 9, the thigh in 11 and 8, and the knee in 5 and 7.

Time–signal intensity curve analysis showed that contrast agent uptake in the nerves of patients with neuropathy was significantly higher compared with normal nerve tissue (Fig. 2).

Patlak analysis could be applied to 27 controls and 42 patients (Fig. 3). Quantitative read-out parameters were compared between patients and controls (Fig. 4). Mean contrast uptake was significantly increased in patients (1.29 ± 0.15 in patients vs 1.18 ± 0.08 in controls; P < 0.001). Likewise, Ktrans was significantly higher in patients (0.046 ± 0.025 vs 0.026 ± 0.016 min⁻¹; P < 0.001). The increase in NBV in patients did not reach statistical significance (3.9 ± 2.6 vs 3.0 ± 1.9 mL/100 mL; P = 0.12).

Subgroup analyses for neuropathies with different etiologies were performed. All 3 read-out parameters were significantly higher in traumatic nerve injury than in any other group (Table 2). Average perfusion parameter values in entrapment neuropathies were found to fall in the range of control subjects and not in that of neuropathies of other etiologies.

The ROC analysis was performed to assess the potential of perfusion read-out parameters as diagnostic markers for the presence of peripheral neuropathy. Whereas NBV was found to be a weak marker, MCU and Ktrans provided considerable diagnostic accuracy for the detection of peripheral neuropathy (ROC values are given in Fig. 5). Since values in entrapment neuropathies fell in the range of controls and not in that of neuropathies of other etiologies, their exclusion yielded improved diagnostic accuracy (Table 3).

Perfusion parameter values were independent of the body region in which they were assessed in healthy controls; for example, no statistically significant differences were found between proximal versus distal locations or between upper and lower extremities. Because

Statistical Analysis

Data visualization and statistical analyses were performed using Origin Pro 9.0 (Northampton, MA). Mean values were calculated for MCU, Ktrans, and NBV in each subject for each nerve. In controls, if more than 1 nerve was present in the imaging sections, values were averaged. In patients, only those nerves affected by neuropathy, that is, those with objectifiable symptoms and/or electrophysiological evidence of dysfunction, were averaged and used for statistical analysis of patients. Graphs mapping the time–signal intensity curves for group mean values and box plots for Ktrans and NBV were charted in Origin Pro 9.0. Mean values were tested against each other for statistical significance using a 2-tailed Student’s t test, with a P value of <0.05 considered significant. The Bonferroni-Holm correction was used to adjust for the family-wise error rate in multiple comparisons. Pearson correlation analysis was performed for age versus MCU, Ktrans, and NBV. Receiver operating characteristic (ROC) analysis was performed in Origin Pro 9.0.

Overall, by time–signal intensity curve analysis and Patlak quantitative analysis, 3 quantitative read-out parameters were calculated for each nerve (Fig. 1) and used for further statistical analysis.

FIGURE 1. Quantitative analysis of peripheral nerve perfusion. Precise regions of interest were drawn around the epineurial contour of peripheral nerves in axial T1-vibe source images as illustrated in the upper left corner. T2- and T1-weighted images were used as reference if exact delineation of nerves was unclear in T1-vibe. Quantitative analysis was performed by time–signal intensity course analysis, which yielded a value for MCU, normalized to baseline before bolus arrival. Quantitative parameter maps were calculated using the Patlak model and yielded values for Ktrans and NBV.

FIGURE 2. Time–signal intensity curve analysis of healthy controls and patients with neuropathy. Values are normalized to baseline before contrast (time points = −7 to −1). Contrast arrival in the arterial system is at time point = 0. Patients with neuropathy show distinctly increased uptake already within the first frames, which persists for more than 2 minutes.
Peripheral nerves are known to show age-related degenerative changes and blood volume is known to decrease with age in the CNS, correlation analyses between perfusion parameters and age were performed. In healthy controls, this revealed a negative linear correlation between NBV and age (\(P = 0.047\)) (Fig. 6). No significant correlations of age with \(K_{\text{trans}}\) or MCU were observed.

DISCUSSION

We here report a DCE MRI technique to characterize peripheral nerve perfusion by parameters of contrast uptake, blood-nerve permeability (\(K_{\text{trans}}\)), and NBV. These measures represent hitherto unused metabolic markers for human neuropathies and seem particularly promising to diagnose and understand nerve diseases for which nerve conduction studies assessing electrophysiological function have previously been the only investigative method. In addition to being the first investigation to test the feasibility of this method, our study also demonstrates that in a total of 59 patients and 43 controls, perfusion parameters are significantly altered in the presence of neuropathy.

We found that symptomatic nerves demonstrate significantly increased contrast enhancement and that this is caused by an increase in \(K_{\text{trans}}\) and not in NBV. This corresponds to a disruption of the BNB, which, under normal circumstances, forms a tight and highly regulated interface in the human body similar to the blood-brain barrier.\(^9\) Evaluation of time-dependent signal increase after contrast administration showed a relatively slow and continuous influx of contrast agent to peripheral nervous tissue during the sequence acquisition. This observation allowed use of the Patlak model for further analysis as a well-known model for quantifying the unidirectional influx constant for low-permeating substances.\(^{12}\) The values we report here for \(K_{\text{trans}}\) and NBV in control nerves are similar to values in normal CNS white matter reported in the literature. For example, Leenders et al.,\(^{13}\) in a study using positron emission tomography, found a cerebral blood volume (CBV) of 2.7 mL/100 mL, which is close to the 3.0 mL/100 mL we report for healthy peripheral nerves. Other studies using DCE T1 MRI arrive at similar values for CBV.\(^{14-16}\) The reported increase in permeability in patients with neuropathy in this study is plausible given the pathophysiological processes in neuropathy with edema and permeability increase of the BNB, demyelination, and axon loss.\(^{10}\) The increase in NBV and permeability in neuropathies is analogous to increases in inflammatory brain lesions detected by DCE MRI\(^{16,17}\) and suggest that the technique as used here yields accurate estimates for perfusion parameters.

In addition to these findings, a trend of decreasing NBV with increasing age was observed in our control group. Little experimental
Perfusion parameters are given for each subgroup of neuropathy patients according to etiology. Subgroup values were tested against controls and against the mean of all other neuropathy patients.

\( P \) values are adjusted for multiple comparisons by the Bonferroni-Holm correction. Numbers in parentheses indicate total number of subjects and number of subjects excluded from the analysis because of insufficient AIF or pulsation artifacts for accurate calculation of \( K_{\text{trans}} \) and NBV.

MCU indicates mean contrast uptake; \( K_{\text{trans}} \), blood-nerve permeability; NBV, nerve blood volume; AIF, arterial input function.

and clinical evidence exists about peripheral nerve perfusion changes associated with aging. Thickening of basal lamina ensheathment during aging has been reported\(^{18} \) as well as a decreasing response to vaso- dilators,\(^{19} \) both of which could factor into decreasing intraneural blood volume during aging. For the CNS, correlations between perfusion parameters and age have been established using positron emission to- mography.

Several groups have investigated the potential of sonography to assess nerve perfusion,\(^{22,23} \) although technical advances and post-processing will enhance the application of sonography for measuring perfusion parameters in nerves.\(^{26} \) The use of sonography has, until now, been limited to measuring intraneural flow, whereas MRI data allow calculation of both permeability and blood volume. In addition, sonography was applied in these studies only in superficial entrapment neuropathies, while nerves frequently affected by polyneuropathies and located deep within tissue, such as the sciatic nerve, are difficult to examine. Moreover, sonography is highly operator dependent. In contrast, MRI allows an observer-independent and fully quantitative analysis.

The diagnostic accuracy calculated by ROC analysis showed perfusion measures to be diagnostic signs of moderate to good accuracy in detecting peripheral neuropathy. In this range, they are comparable with the diagnostic accuracy of diffusion tensor imaging as the hitherto only available functional imaging method for the PNS.\(^{27} \) Refinement of the used sequence and postprocessing may yield even better diagnostic quality. We anticipate that perfusion MRI for peripheral nerves will find application in the investigation of the time course and localization of the highly prevalent and poorly understood diseases such as inflammatory and ischemic polyneuropathies. Furthermore, the technique may also prove useful in monitoring of therapeutic drug effects in the polyneuropathies.

Our study has several limitations. First, the general assumptions and limitations of the Patlak model apply to the technique, including unidirectionality of permeability at least in the first 2 minutes. Second, a number of patients were excluded from evaluation of \( K_{\text{trans}} \) and NBV, either because AIF did not allow calculation or because of pulsation artifacts. Further refinement of sequence parameters to improve AIF measurement and of software parameters may solve this in the future. Third, absolute values as reported here are always dependent on the model chosen; thus, investigators should verify a normal range of values at their own centers.\(^{28,29} \) Finally, our study consisted of a large

![FIGURE 5. ROC analysis. Parameters of MCU and \( K_{\text{trans}} \) have significant diagnostic accuracy in discriminating neuropathies from healthy controls with AUC of 0.78 and 0.77, respectively.](image)
but heterogeneous patient group. Although this was effective to test the technique at different anatomical positions and in different forms of neuropathy, future investigations may focus on 1 restricted diagnosis or etiology.

In conclusion, we have developed a method for quantification of peripheral nerve perfusion parameters. The plausibility of the technique is supported by findings in healthy controls and in a large number of patients with neuropathy. Dynamic contrast-enhanced T1 MRI may be used in future investigations on peripheral neuropathy and in clinical MRN.

REFERENCES