Original Investigation

Nerve Fascicles and Epineurium Volume Segmentation of Peripheral Nerve Using Magnetic Resonance Micro-neurography

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Rationale and Objectives: The aims of this study were to propose a semiautomated technique to segment and measure the volume of different nerve components of the tibial nerve, such as the nerve fascicles and the epineurium, based on magnetic resonance microneurography and a segmentation tool derived from brain imaging; and to assess the reliability of this method by measuring interobserver and intraobserver agreement.

Materials and Methods: The tibial nerve of 20 healthy volunteers (age range = 23–69; mean = 47; standard deviation = 15) was investigated at the ankle level. High-resolution images were obtained through tailored microneurographic sequences, covering 28 mm of nerve length. Two operators manually segmented the nerve using the in-phase image. This region of interest was used to mask the nerve in the water image, and two-class segmentation was performed to measure the fascicular volume, epineurial volume, nerve volume, and fascicular to nerve volume ratio (FNR). Interobserver and intraobserver agreements were calculated.

Results: The nerve structure was clearly visualized with distinction of the fascicles and the epineurium. Segmentation provided absolute volumes for nerve volume, fascicular volume, and epineurial volume. The mean FNR resulted in 0.69 with a standard deviation of 0.04 and appeared to be not correlated with age and sex. Interobserver and intraobserver agreements were excellent with alpha values >0.9 for each parameter investigated, with measurements free of systematic errors at the Bland-Altman analysis.

Conclusions: We concluded that the method is reproducible and the parameter FNR is a novel feature that may help in the diagnosis of neuropathies detecting changes in volume of the fascicles or the epineurium.

Key Words: MRI; nerve; micro; neurography; segmentation.

INTRODUCTION

Peripheral nerve pathology reflects in a variety of histopathologic patterns. The Seddon classification is traditionally used to divide acute nerve injuries into neuroapraxia (axonal strain with temporary functional loss), axonotmesis (axonal cut short with Wallerian degeneration), and neurotmesis (discontinuity also of the supporting connective tissues) (1,2). Chronic neuropathies are associated with additional modifications such as collagen deposition on the extracellular matrix, basement membrane thickening and changes in volume of the connective sheaths (ie, the epi-, peri- and endoneurium), nerve fibers loss, demyelination, remyelination, and Schwann cell proliferation (3).

The assessment of peripheral nerve disorders is achieved through medical history and physical examination, supported by instrumental investigations including electrophysiology, nerve biopsy, and magnetic resonance imaging (MRI). Electrophysiology detects gross distribution of nerve dysfunction, but it is limited for determining the exact location of nerve injury and cannot depict morphological alterations within the nerve (4). Histopathology may be carried out in vivo with the biopsy of the sural nerve, which can be sacrificed in restricted circumstances. Furthermore, the sural nerve contains only sensitive fibers and the specimens may not necessarily represent the underlying disease (4). MRI is the most advanced imaging technique available for the study of peripheral nerves, with the advantages to be noninvasive and repeatable (5–7). Standard protocols for MRI of peripheral nerves, also known as magnetic resonance (MR) neurography

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(8,9), include high-resolution axial T1-weighted and fat-suppressed T2-weighted images (4). As injured nerves appear hyperintense on T2-weighted images, several studies have focused on the increased T2 relaxation time to evaluate the nerve damage (10–12). However, the morphological detail usually achieved is insufficient for visualization of the single nerve fascicles and the tissues within and around.

The issue of spatial resolution may be overcome by techniques of MR microscopy, known as MR micro-neurography as a whole, that have been developed for at least two decades but still lack appropriate applications in the clinical practice. Early experiments were performed on cadaveric specimens with high-field scanners (up to 3 Tesla) and dedicated small coils, using a field of view of 1–1.5 cm wide and reaching a pixel resolution of 40–60 μm, enough to visualize the perineurium surrounding the single nerve fascicles (13–15). Nowadays, the challenge is to achieve such a similar resolution in vivo, with clinical MR scanners and readily available coils and sequences. Some of the intrinsic structures of peripheral nerves may be already demonstrated using a variety of high-resolution MRI techniques (16–20), and for peripheral nerves, such as the tibial and the common fibular nerves, it is possible to reach a pixel resolution of 100–120 μm in a reasonable time of scan (21). In these conditions, the nerve fascicles can be discerned from the epineurium and the perineurium. There is histologic data that morphologic changes in neuropathies occur also at this scale level, eg, in diabetic neuropathy variation in diameter of the nerve fascicles or thickness of the perineurium and the epineurium has recently been reported (22).

The in vivo quantitative evaluation of morphological parameters using MRI has become an important diagnostic and prognostic tool in many medical fields, most notably in neurology. Several segmentation techniques have emerged and are now routinely used for the semi-automatic evaluation of volume changes in the central nervous system (CNS) (23), giving researchers and physicians invaluable information not otherwise appreciable. However, the use of those techniques in the peripheral nervous system setting has yet to gain traction, probably because of the significant intersubject anatomical variability and the technical difficulties related to the small dimensions of peripheral nerves. Thus, MR microneurography has the potential to become a major diagnostic or prognostic tool in peripheral neuropathies if these changes in nerve internal structure are assessed and quantified.

In this paper, we propose a reproducible protocol of MR microneurography to demonstrate the internal architecture of peripheral nerves in vivo, for the study of the posterior tibial nerve, using a clinical 3 Tesla scanner and a standard set of coils and sequences. Relying on the spatial resolution achieved through this protocol, we describe a semiautomated technique of segmentation and measurement of the volume of different nerve components, such as the nerve fascicles and the epineurium. Our segmentation technique is based on the tool FSL (FMRIB Software Library) FAST (FMRIB's Automated Segmentation Tool, the Analysis Group, Center for Functional MRI of the Brain, Oxford, UK) (24), which is routinely used for brain segmentation but, to the best of our knowledge, it has never been employed for peripheral nerve segmentation (24). Our objectives are (i) to visualize the different nerve components and quantify their volume in the distal portion of the posterior tibial nerve in normal subjects, and (ii) to verify the reliability of our method assessing the inter- and intraoperator agreement.

MATERIALS AND METHODS

Subjects

The ethical committee of our institution approved the study, and all subjects provided written informed consent. A total of 20 healthy volunteers (13 men, 7 women; age range = 23–69, mean = 47, standard deviation [SD] = 15) were recruited from hospital employees and the local community. A short history was obtained, and neurological examination was performed. The subjects were excluded if they had either clinical evidence or past history of lumbar roots compression (monolateral pain, proximal with distal progression), peripheral polyneuropathy, tarsal tunnel syndrome, diabetes mellitus, major trauma, or surgery in the lower leg. See Table 1 for details on the subjects.

Imaging Protocol

All studies were performed on a Discovery MR750 3T scanner (GE Healthcare, Milwaukee, WI, USA) using a six-channel carotid array coil, which was manually adapted and fixed by the sides of the ankle region. The examinations were focused on the posterior tibial nerve; right and left limbs were imaged in every subject. The first sequence we used was a 3D SPGR (Spoiled Gradient Echo) with standard fat suppression; the field of view was a cube with 14 cm of side, voxel size of 1 mm^3, and time of scan approximately 2 minutes, as already described (21). This sequence allowed to precisely locate the posterior tibial nerve, and multiplanar reconstruction (MPR) was used to select a perpendicular plane to the nerve axis. A second sequence with higher resolution was applied with a field of view located approximately 2 cm above the medial malleolus in a straight tract of the nerve, in the aim to obtain axial images always perpendicular to the main nerve axis and

TABLE 1. Mean Age with Standard Deviation (SD) of the Subjects Included in the Study Divided by Gender

Gender	Subjects	Age Mean	SD
Males	13	42.9	14.8
Females	7	50.3	13.8
Total	20	45.3	14.6