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Differences in Quantitative Architecture of Sciatic Nerve May Explain Differences in Potential Vulnerability to Nerve Injury, Onset Time, and Minimum Effective Anesthetic Volume

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Background: In sciatic nerve (SN) blocks, differences are seen in risk of nerve damage, minimum effective anesthetic volume, and onset time. This might be related to differences in the ratio neural:nonneural tissue within the nerve. For the brachial plexus, a higher proximal ratio may explain the higher risk for neural injury in proximal nerve blocks. A similar trend in risk is reported for SN; however, equivalent quantitative data are lacking. The authors aimed to determine the ratio neural: nonneural tissue within SN *in situ* in the upper leg.

Methods: From five consecutive cadavers, the region between the sacrum and distal femur condyle was harvested and frozen. Using a cryomicrotome, consecutive transversal sections (interval, 78 μm) were obtained and photographed. Reconstructions of SN were made strictly perpendicular to its long axis in the midgluteal, subgluteal, midfemoral, and popliteal regions. The epineurial area and all neural fascicles were delineated and measured. The nonneural tissue compartment inside and outside SN was also delineated and measured.

Results: The amount of neural tissue inside the epineurium decreased significantly toward distal (midfemoral/popliteal region) ($P < 0.001$). The relative percentage of neural tissue decreased from midgluteal ($67 \pm 7\%$), to subgluteal ($57 \pm 9\%$), to midfemoral ($46 \pm 10\%$), to popliteal ($46 \pm 11\%$). Outside the SN, the adipose compartment increased significantly toward distal ($P < 0.007$).

Conclusion: In SN, the ratio neural:nonneural tissue changes significantly from 2:1 (midgluteal and subgluteal) to 1:1 (midfemoral and popliteal). This suggests a higher vulnerability for neurologic sequelae in proximal SN, and may explain differences observed in minimum effective anesthetic volume and onset time between proximal and distal SN blocks.

NERVE injury after application of peripheral nerve blocks is a relatively uncommon but feared complication. Among several etiologic factors, intraneural injection is generally considered a major risk factor for neurologic sequelae.[1–4] Although the exact mechanism is still unclear, factors such as toxicity, ischemia, high

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injection pressure, and direct mechanical injury have been postulated as possible contributors.[5–7] Despite the increasing use of ultrasound, the occurrence of intraneural injection is still reported.[8,9]

Recent findings suggest that intraneural injection does not invariably cause neural injury.[8,10,11] One of the mechanisms that would explain this observation might be related to the microarchitecture of the peripheral nerve. In an earlier study, the authors showed that the distribution of neural to nonneural tissue inside the epineurium changed between proximal (interscalene) and distal parts (shoulder) of the brachial plexus.[12] For the brachial plexus *in situ*, the ratio of neural to nonneural tissue increased from 1:1 proximal to 1:2 distal toward the shoulder. In addition, toward distal, an increasing amount of fat and connective tissue was observed outside the brachial plexus.

Based on the estimated rate of occurrence of nerve injury after peripheral nerve block, almost twice as many nerve injuries are seen in proximal brachial plexus (interscalene) blocks compared with distal brachial plexus (axillary) blocks.[13] The higher ratio of neural to nonneural tissue in proximal parts of the brachial plexus might be one of the possible explanations of this increased risk. For the sciatic nerve, a similar trend in distribution of risk is reported.[13] However, equivalent quantitative data about the *in situ* ratio of neural to nonneural tissue inside the epineurium and the amount of adipose and connective tissue surrounding the epineurium of the sciatic nerve are lacking.

We hypothesize that the ratio of neural to nonneural tissue inside the sciatic nerve shows the same trend as found for the brachial plexus,[12] *i.e.*, a decrease toward distal. To evaluate this hypothesis, we determined *in situ* the ratio of neural to nonneural tissue within the sciatic nerve in the four major sciatic nerve block areas in the upper leg: midgluteal, subgluteal, midfemoral, and popliteal. Quantitative data of the sciatic nerve based on high-resolution, cross-sectional images were acquired. In addition, in the same areas the amount of adipose and connective tissue surrounding the sciatic nerve was determined.

Materials and Methods

After institutional review board approval (University Medical Center Utrecht, Utrecht, The Netherlands), five

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Table 1. Baseline Characteristics of the Cadavers

Specimen	Age, y	Sex	Weight, kg	Height, cm	BMI, kg/m^2
L I	98	Female	50	150	22.2
R II	82	Female	56	155	23.3
R III	82	Male	71	196	18.5
R IV	91	Male	73	188	20.7
R V	86	Female	73	176	23.6

BMI = body mass index; L = left specimen; R = right specimen.

upper legs of five different cadavers (table 1) were obtained from the Department of Anatomy of the University Medical Center Utrecht. The investigated cadavers did not have any known comorbidities affecting their nerves. The upper legs contained the regions between the sacrum and distal femur condyle. The exact methods used for preparation are explained elsewhere.[12] In short, the legs were frozen in carboxymethylcellulose gel at $-30°$C. Using a heavy-duty sledge cryomicrotome (PMV 450; LKB Instruments, Stockholm, Sweden), consecutive transversal sections (interval, 0.078 mm) of each specimen were obtained. The surface of each section was photographed (Nikon D1X; Nikon Corporation, Chiyoda-ku, Tokyo, Japan) at a resolution of 300 pixels/inch. The exact dimensions of the part of the specimen that appeared on the photographed image were noted. In total, 8,000–9,600 images per specimen were collected. Based on the obtained transversal cross sections, the coronal and sagittal planes were reconstructed using Enhanced Multiplanar-reformatting Along Curves software (E-MAC®-group, Department of Information and Computing Sciences, University of Utrecht, Utrecht, The Netherlands). For each upper leg, three digital datasets were obtained, each set comprising approximately 14.9 gigabytes.

Per region, five locations perpendicular to the long axis of the sciatic nerve were reconstructed. Each location contained a center site (midpoint) and locations 5 and 10 mm proximal and distal to each midpoint (fig. 1A). In the midgluteal region, the midpoint was the first reconstructed image where the sciatic nerve emerged inferior to the piriformis. As the midpoint of the subgluteal region, the site was chosen at which the sciatic nerve passes the caudal edge of the gluteus maximus. The midfemoral midpoint was the middle of the line between the greater trochanter of the femur and the popliteal crease. To identify this point, the surface of the skin was marked with red dye before sectioning. Finally, as the midpoint of the popliteal region, the most distal part of the unified sciatic nerve was chosen, just before its division into the tibial and common peroneal nerve. Therefore, a total of 100 digital perpendicular reconstructions were created. In each of the reconstructed images, the epineurial surface area was delineated and measured using the public domain image processing program ImageJ 1.40 g (National Institutes of Health,
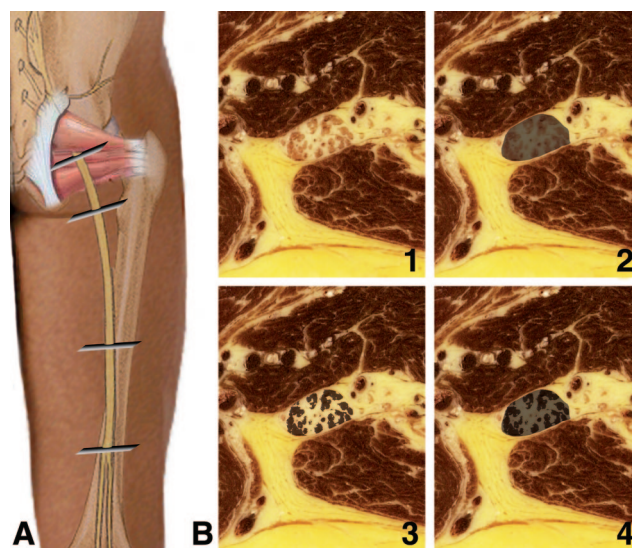
Fig. 1. (*A*) Schematic diagram showing the location of midgluteal, subgluteal, midfemoral, and popliteal sciatic nerve. (*B*) Representative reconstructions perpendicular to the long axis of the sciatic nerve demonstrating how measurements were conducted. (*1*) Original image; (*2*) demarcated total epineurial tissue (*shaded in gray*); (*3*) demarcated neural tissue, that is, perineurium and nerve fascicles (*black dots*); and (*4*) combined image showing both measurements superimposed.

Bethesda, MD). When the continuity of the epineurium was not fully visible in one image, a rapid sequential display of consecutive images was used to identify the epineurium. All individual neural fascicles with their perineurium were labeled separately using contrast enhancement and thresholding. Through automated pixel counting, the sum of the surface areas was calculated in square millimeters and was defined as neural tissue (fig. 1B). The remaining surface area within the sciatic nerve was defined as nonneural tissue and was calculated by subtracting the total surface area of the fascicles from the total surface area of the epineurium.

The borders of the adipose tissue compartment surrounding the sciatic nerve were identified using muscular borders and fascial layers (fig. 2). In the midgluteal region (fig. 2A), the borders were formed as follows: anteriorly by the internal obturator, laterally by the fascia of the piriformis and the gluteus medius, posteriorly by the gluteus maximus, and medially by the distinctive fascial layer within the adipose tissue. In the subgluteal region (fig. 2C), the borders were defined anteriorly by the adductor magnus, laterally by the femur and the adjacent border of gluteus maximus, posteriorly by the long head of biceps femoris and the adjacent border of gluteus maximus, and medially by the adductor magnus and the tendon of semimembranosus. In the midfemoral region (fig. 2E), the muscular borders were defined anteriorly by the adductor magnus, laterally by the vastus lateralis, posteriorly by the long head of biceps femoris, and medially by the semimembranosus and semitendinosus. Finally, in the popliteal region (fig. 2G), the bor-
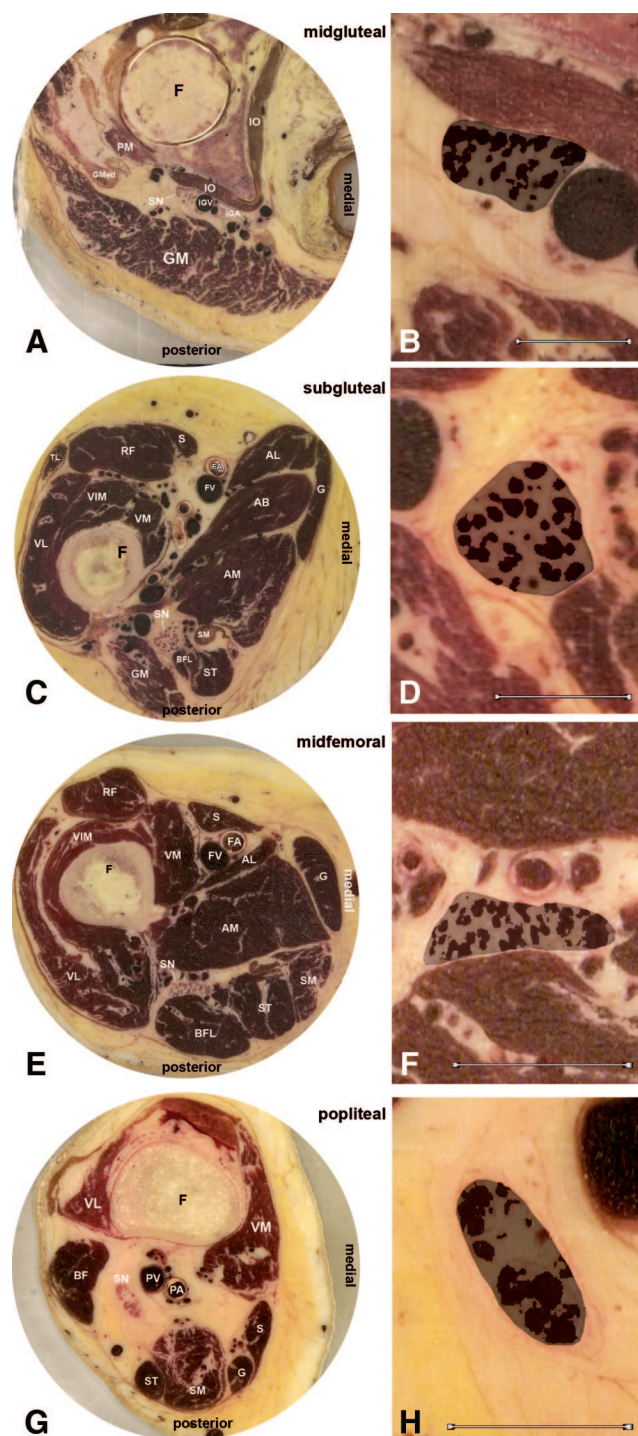
Fig. 2. Overview of the investigated areas (*left*) with details of the demarcated neural contents (*right*; *black dots*) and epineurial areas (*gray fields*). (*A* and *B*) Midgluteal; (*C* and *D*) subgluteal; (*E* and *F*) midfemoral; (*G* and *H*) popliteal. *Bar* = 10 mm. AB = adductor brevis; AL = adductor longus; AM = adductor magnus; BF = biceps femoris; BFL = biceps femoris long head; F = femur; FA = femoral artery; FV = femoral vein; G = gracilis; GM = gluteus maximus; GMed = gluteus medius; IGA= inferior gluteal artery; IGV = inferior gluteal vein; IO = internal obturator muscle; PA = popliteal artery; PV = popliteal vein; PM = piriformis; RF = rectus femoris; S = sartorius; SM = semimembranosus; SN = sciatic nerve; ST = semitendinosus; TL = tensor fasciae latae; VIM = vastus intermedius; VL = vastus lateralis; VM = vastus medialis.

ders were defined anteriorly by the femur, laterally by the biceps femoris and fascia poplitea, posteriorly by the semimembranosus, semitendinosus, and fascia popliteal/lata, and medially by the semimembranosus, gracilis, sartorius, and vastus medialis. The area within these adipose tissue compartments was demarcated and measured.

Statistical Analysis

In all specimens, the means ± SDs of all values in the same region (midpoint, 5 and 10 mm proximal, and 5 and 10 mm distal to the midpoint) were calculated. Therefore, 5 measurements per region were conducted, comprising a total of 20 measurements per cadaver. Comparison of differences in cross-sectional areas between the regions (midgluteal, subgluteal, midfemoral, and popliteal) and within the same subjects (n = 5) was determined by repeated-measures analysis of variance, with Bonferroni correction. SPSS (version 17.0.0; SPSS Inc., Chicago, IL) was used for statistical analysis. For statistical significance, a value of $P < 0.05$ was chosen.

Results

Figure 2 shows in detail reconstructed images of the sciatic nerve in the midgluteal, subgluteal, midfemoral, and popliteal regions. An overview of the absolute and relative cross-sectional area of neural and nonneural tissue inside the sciatic nerve is presented in table 2. All data are presented as mean ± SD. In the proximal region of the sciatic nerve, *i.e.*, midgluteal and subgluteal regions, the absolute amount of neural tissue did not change: 34 ± 5.9 and 33.9 ± 6.0 mm^2, respectively. In the distal region of the sciatic nerve, *i.e.*, midfemoral and popliteal regions, no change in absolute amount of neural tissue was seen as well: 18.4 ± 3.8 and 19.1 ± 4.0 mm^2, respectively. However, the decrease of neural tissue seen between the proximal and distal regions of the sciatic nerve was significant ($P < 0.0001$) (fig. 3A).

The absolute amount of nonneural tissue in the sciatic nerve ranged between 17.2 and 25.9 mm^2 in the proximal region and between 22.6 and 23.7 mm^2 in the distal region. Overall, no significant changes in nonneural tissue inside the epineurium were observed between the proximal and distal parts of the sciatic nerve. However, the increase of nonneural tissue seen between the midgluteal and subgluteal regions was significant ($P < 0.001$).

The percentage of neural tissue inside the epineurium of the sciatic nerve is shown in figure 3B. The highest mean percentage ($66.7 \pm 6.5\%$) was seen in the midgluteal region, whereas the lowest mean percentage ($46 \pm 10\%$) was observed in both the midfemoral and popliteal regions. The significant decrease of percentage ($P < 0.0001$) between the proximal and distal regions was

Table 2. Overview of Absolute and Relative Amount of Neural and Nonneural Tissue inside the Sciatic Nerve and Adipose Tissue outside the Sciatic Nerve

Region	Neural*	Nonneural†	% Neural‡	P Value§	Adipose‖	P Value#
Midgluteal	34.0 ± 5.0	17.2 ± 4.9	66.7 ± 6.5		226 ± 78	
vs. subgluteal				0.004		1.000
vs. midfemoral				0.000		0.000
vs. popliteal				0.000		0.001
Subgluteal	33.9 ± 6.0	25.9 ± 5.3	56.7 ± 8.8		231 ± 57	
vs. midfemoral				0.015		0.000
vs. popliteal				0.012		0.023
Midfemoral	18.4 ± 3.8	22.6 ± 6.8	45.7 ± 9.6		87 ± 34	
vs. popliteal				1.000		0.000
Popliteal	19.1 ± 4.0	23.7 ± 7.3	45.7 ± 10.9		320 ± 101	

All data are presented as mean ± SD. Bonferroni adjustments for multiple comparisons were performed.

* Cross-sectional area of neural tissue inside the sciatic nerve (mm^2). † Cross-sectional area of nonneural tissue inside the sciatic nerve (mm^2). ‡ Relative percentage of neural tissue inside the sciatic nerve (%). § Comparison of relative percentage of neural tissue inside the sciatic nerve between the regions. ‖ Cross-sectional area of adipose tissue outside the sciatic nerve (mm^2). # Comparison of absolute amount of adipose tissue outside the sciatic between the regions.

due not only to an absolute decrease of neural tissue, but also to an increase of nonneural tissue compared with midgluteal values.

The area of the connective tissue compartment (adipose tissue) surrounding the sciatic nerve did not change in the proximal (midgluteal/subgluteal) area of the sciatic nerve, being around 230 mm^2. From subgluteal to midfemoral, the amount of adipose and connective tissue decreased significantly to its lowest value, 87 mm^2. In the popliteal region, the amount of adipose and connective tissue reached its highest value, 320 mm^2. Also, between the proximal (midgluteal) and distal (popliteal) regions of the sciatic nerve, the amount of connective tissue outside the sciatic nerve increased significantly. Table 2 presents the amount of adipose tissue outside the sciatic nerve and the changes between the regions (fig. 3C).

Discussion

This is the first study that addresses the quantitative architecture of the sciatic nerve *in situ*. In relatively undisturbed anatomy provided by cryomicrotomy, we found differences in absolute and relative amounts of neural and nonneural tissue between the major sites of sciatic nerve block. The absolute amount of neural tissue decreased from proximal to distal (34 mm^2 to 19 mm^2, respectively), whereas the nonneural tissue remained about the same (17 to 22 mm^2). This decrease is attributed to the muscular branches to the upper leg muscles that branch off in this trajectory.[14] Consequently, the ratio of neural to nonneural tissue changed, from proximal to distal, from 2:1 to 1:1. Furthermore, the amount of adipose tissue surrounding the sciatic nerve was significantly higher in the popliteal region, compared with proximal areas.

These findings may have implications for our understanding of sciatic nerve blocks. In this respect, three parameters are of particular interest: possible risk of nerve injury after sciatic nerve block, minimum effective anesthetic volume (MEAV) required for a successful nerve block, and duration of onset time. These parameters are generally used to compare various approaches of nerve blocks; however, it is usually unclear which factors would explain variations observed in these parameters. We believe that part of the explanation could be found in the varying amount of neural and nonneural tissue, inside as well as outside the sciatic nerve.

The observed differences in the ratio of neural to nonneural tissue may explain reported differences in risk of nerve injury between proximal and distal parts of the sciatic nerve. A twofold difference of the estimated rate of nerve injury has been reported between proximal and distal sciatic nerve blocks.[13] For proximal blocks (gluteal region), the estimated rate of occurrence of neuropathy is 0.41% (95% confidence interval, 0.02–9.96), compared with 0.24% (95% confidence interval, 0.10–0.61) for distal (popliteal region) blocks.[13] A similar difference in ratio of neural to nonneural tissue and rate of occurrence of neuropathy was found for the brachial plexus between proximal and distal parts.[12,13] We speculate that a low ratio of neural to nonneural tissue is a protective factor against the occurrence of neuropathy after intraneural injection.

Further, recent findings suggest that intraneural injection or intraneural catheterization with small amounts of local anesthetic does not invariably cause neural injury.[8,10,11,15] Injection inside the perineurium is associated with high injection pressures and leads to fascicular injury and neurologic deficit, whereas injection inside the epineurium results in low initial pressures with return of normal motor function.[5] Even with the use of sharp needles, it is suggested that intraneural needle insertion will more commonly result in interfascicular rather than intrafascicular needle placement.[16] Because the perineurium, in contrast to the epineurium,
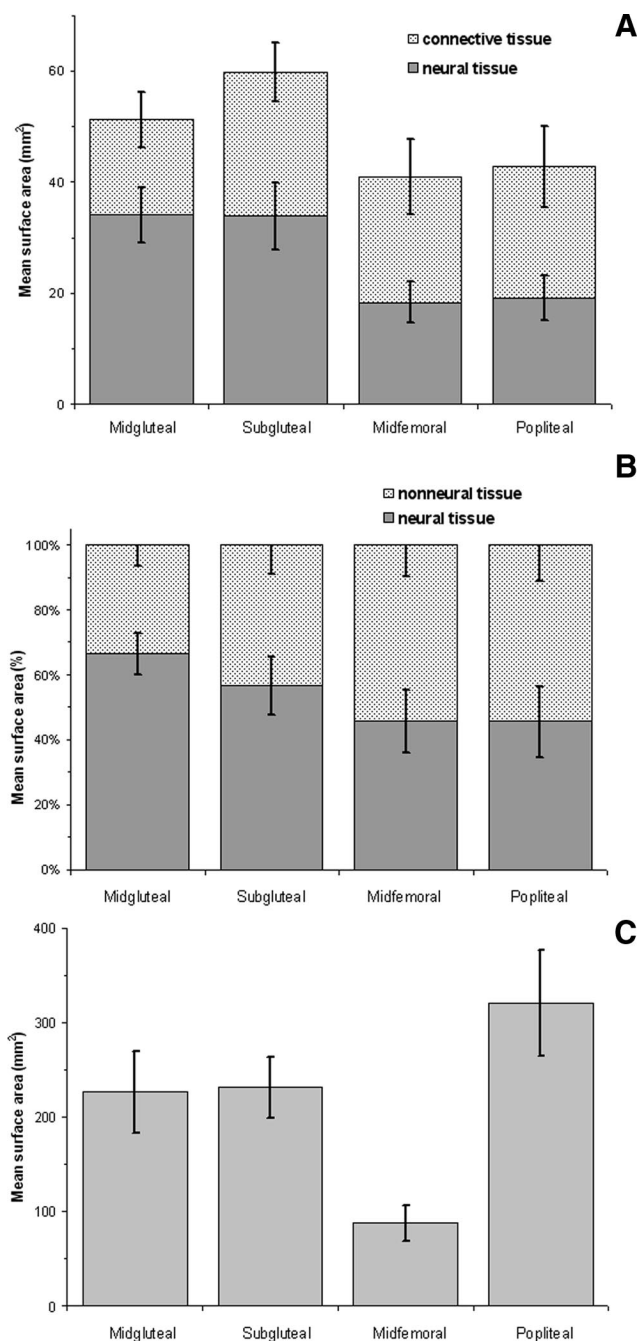
Fig. 3. Measured areas in the midgluteal, subgluteal, midfemoral, and popliteal regions of all upper legs. (*A*) Absolute values (mm²) of neural and nonneural (connective) tissue inside the epineurium (means ± SDs). (*B*) Relative values (percentages) of neural *versus* nonneural tissue inside the epineurium (means ± SDs). (*C*) Absolute values (mm²) of adipose/connective tissue compartment surrounding the sciatic nerve.

is a tough and mechanically resistant tissue,[17] it is unlikely that a blunt needle will penetrate it easily. In addition, we believe that the nonneural tissue both inside and outside the sciatic nerve may serve as a protective layer against nervous tissue injuries.

Nonetheless, other factors besides the proportion of neural to nonneural tissue should be considered in the etiology of neurologic sequelae. These include proce-

dure-related factors (*i.e.*, injection pressure, type of needle, local anesthetic toxicity, manipulation of nervous tissue, high-risk surgery) and patient-related factors (*i.e.*, epineural and perineural vascularization, patient comorbidities). Clinical evidence suggests that patients with preexisting peripheral nerve injury are more likely to sustain further nerve damage if a second subclinical or obvious injury occurs.[18,19] The presence of one or more of these factors could increase the risk of neuropathy, irrespective of the location of the nerve block.

Our findings may further explain the differences in MEAV and onset time observed between proximal and distal sciatic nerve blocks. In a prospective, randomized trial, Taboada *et al.*[20] reported a larger volume of local anesthetic for the popliteal sciatic nerve block compared with the subgluteal approach. Similar results were found by Cappelleri *et al.*[21] In addition, an observational study comparing posterior gluteal and lateral popliteal sciatic nerve block reported faster onset of sensory block in favor of the gluteal sciatic nerve block.[22] Also, for the subgluteal sciatic nerve block, significantly faster onset time of sensory and motor blockade was seen compared with the popliteal approach.[23,24] Furthermore, with less injected volume, a faster onset time and higher success rate were observed in a proximal approach compared with a more distal approach.[25] However, while Kilpatrick *et al.*[26] reported a better success rate with the midgluteal approach compared with the popliteal approach (95% *vs.* 45% of patients; $P < 0.01$), no difference in onset time was noted. Although this could reflect the true situation, this study was underpowered by the small amount of included subjects.

We found no difference of neural-to-nonneural ratio between the midfemoral and popliteal region. However, significantly more adipose and connective tissue was found outside the sciatic nerve in the popliteal region. This latter observation could play a role in the amount of local anesthetic required for a successful block. In one of the few studies comparing midfemoral with popliteal sciatic nerve block, Triado *et al.*[27] found significantly shorter onset time of sensory block in the midfemoral group compared with the popliteal group.

It seems that the popliteal region is associated with the highest amount of MEAV and the longest onset time. Parallel to this, the lowest ratio of neural to nonneural tissue was found in the midfemoral and popliteal regions. In addition, the largest amount of adipose and connective tissue surrounding the sciatic nerve was observed in the popliteal region. We speculate that the observed differences in MEAV and onset time are related to the amount of nonneural tissue inside and outside the sciatic nerve. The nonneural tissue serves as a reservoir for lipophilic local anesthetics. Therefore, more time is needed to reach the neural tissue because less local anesthetic is available to diffuse across the epineurium to block the fascicles. At the same time, the percentage of

nonneural tissue inside the nerve is increased, which acts as a diffusion barrier and eventually slows down the diffusion rate of the local anesthetic to reach the fascicles if it is not injected in the vicinity of the fascicles. These factors would lead to a slower onset time and a higher MEAV in the distal part of the sciatic nerve.

In an early dissection study, different values were found for the percentage of cross-sectional area of nervous tissue.[28] In fact, the ratio of neural to nonneural tissue increased slightly, from proximal to distal, from approximately 1:2 to 1:1. The observed differences particularly in the proximal parts are most probably explained by the differences in techniques used, *i.e.*, undisturbed anatomy *versus* microdissection. We believe that the use of undisturbed anatomy in combination with histology, digital sampling, and automated measurements provides a more accurate and detailed identification and demarcation of all structures.

Our study has some important limitations, which makes it necessary to use caution in extrapolating the data to the clinical field. Even with the use of undisturbed anatomy, flawless comparison between postmortem examination and living individuals is impossible. The number of specimens used in our report is small, partly because of the elaborate work in obtaining, processing, and reconstruction of the large amount of images. Furthermore, their age is rather high. This could limit the extrapolation of the data to the younger population. Studies on nerve conduction indicate that nerve conduction velocity decreases with age.[29] This is supported by anatomical evidence demonstrating a reduced number of nerve fibers with aging.[30,31] A flawless comparison between the elderly and young individuals is therefore not possible. However, because these changes are observed throughout the course of the nerves and the values are compared within the same subjects, we believe that the provided relative percentages and ratios in our analysis are still accurate.

In addition to the previous limitations, the values for the adipose compartment outside the sciatic nerve should be tested *in vivo* by injection of stained solutions in cadavers to study the spread of local anesthetics in patients. Therefore, our assumptions need to be confirmed in further studies. However, in our opinion, the data seem to be reliable because the proximal–distal trend for neural and nonneural tissue was similar in all investigated specimens. In addition, no large differences in measured values were observed between the specimens.

Cryomicrotomy was used because it is considered the gold standard for examining undisturbed topography of nerve structures.[12,32] Advantages of this method are examination and measurement of dimensions and surfaces without altering the topographic relations, which is not the case when dissection is used. Conventional imaging modalities such as computer tomography or magnetic resonance imaging are also helpful to examine undisturbed anatomy, preferably in living individuals. However, up to now, their resolution has been limited. In addition, technical limitations such as partial volume effect (*i.e.*, pixel representing more than one kind of tissue type by averaging) do not allow analysis of small regions with different tissue signal intensities.[33,34] A major limitation of cryomicrotomy is postmortem examination of the tissue. This does not take into account the tissue oxygenation, blood circulation, and the elasticity of the structures *in vivo*. Subsequent effects of the muscle tone on the shape and diameter of the sciatic nerve are also diminished. In addition, freezing of the specimens causes minimal shrinkage, with linear dimensions in tissues changing by approximately 2% or less.[35]

In summary, in the sciatic nerve, the ratio of neural to nonneural tissue changes significantly from 2:1 (midgluteal and subgluteal) to 1:1 (midfemoral and popliteal). The findings suggest a higher vulnerability for neurologic sequelae after inadvertent intraneural injection in the proximal parts of the sciatic nerve. In addition, the observed values may explain the differences seen in MEAV and in onset time at different levels of the sciatic nerve.

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