Nerve Identification and Prevention of Intraneural Injection in Regional Anesthesia

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Proefschrift, met een samenvatting in het Nederlands en Arabisch

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Nerve Identification and Prevention of Intraneural Injection in Regional Anesthesia

Het identificeren van zenuwen en de preventie van intraneurale injectie in locoregionale anesthesie

(met een samenvatting in het Nederlands)

تحديد موقع العصب والوقاية من الحقن داخل العصب في التخدير الموضعي

(مع شرح مختصر باللغة العربية)

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To my beloved parents,
brothers and sister,
and to my love

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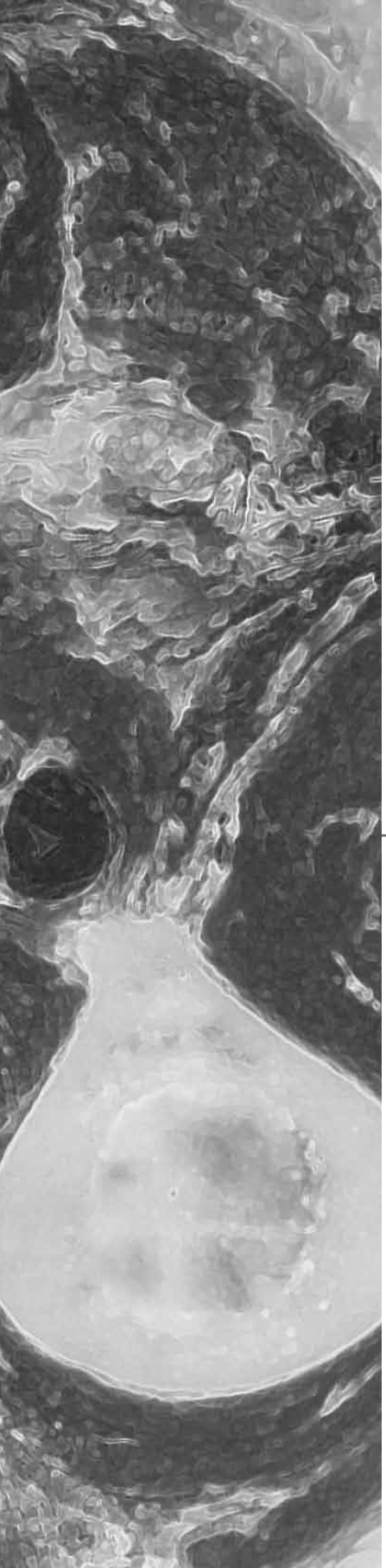

Chapter 1

General Introduction

The practice of nerve blockade dates back until the late 19th century. A major factor in the development of cocaine as a local anesthetic was the paper published in 1880 by Vassily von Anrep, in which he described the pharmacology of cocaine and suggested its use for surgery.[1] In 1884, Karl Koller introduced cocaine as a local anesthetic for eye surgery. In the same period, also, William Halsted and Richard Hall performed nerve blocks, *i.e.,* placing local anesthetic around a nerve to produce anesthesia in the nerve's distribution, as opposed to relying on surface or infiltration anesthesia, which others were using.[2,3] They reported the first successful nerve block of the inferior dental nerve with 4% cocaine solution.[4] In 1892, Schleich published the results of his studies in which he used a 0.1-0.2% solution of cocaine hydrochloride intra- and subcutaneously, introducing the so-called infiltration anesthesia.[5] The real start of regional anesthesia at the level of peripheral nerves like the brachial plexus was described in 1891, when Hirschel and Kulenkampff performed percutaneously a blockade of the plexus.[6-8] During the 20th century, many techniques for upper and lower extremity blocks have been developed, and old approaches have been refined to meet contemporary safety standards, among others by pioneers such as Labat and Winnie.

Refinement of a technique is only useful if it does not bring additional, potential harmful effects on the body; it should even decrease these. When, for example, cocaine was introduced as a potent anestheticum, at the end of the 19th century, it was found that cocaine possessed many undesirable effects, including addiction, which triggered off interest in other, less toxic, anaesthetics.[9] Several complications are known to be caused by the local anesthetic itself and included localized or generalized toxicity and allergic reactions. In addition, complications related to the procedure itself and to the patient's characteristics have been reported, including mechanical or ischemic injury and neurological dysfunction.[10]

As with every other intervention in medicine, evidence based effectiveness, reliability and safety are of vital importance to adopt and continue a new procedure or technique. For peripheral nerve blockades, accuracy of needle tip position, in combination with safe delivery of the local anesthetic are the continuous care of every anesthesiologist. The placement of the needle in such a way that the local anesthetic has its highest effect on the nervous tissue without damaging the nerve is, and will, remain top priority in regional anesthesia. Correct needle placement is highly dependent on knowledge of the topographic anatomy of the nerves and adjacent structures. Furthermore, adequate volumes and dosages of local anesthetics are a prerequisite for a high success rate of peripheral nerve blocks.[11]

Through the history of peripheral nerve blockade, many improvements have been and are still being implemented with regard to needle types, electrical nerve stimulation in stead of paresthesia, and ultrasound. They all share the same purpose: how to find the desired nervous structures without causing damage to them?

At present, the search for effective, reliable and safe nerve blocks in the upper and lower extremity continues. As earlier mentioned, tools like nerve stimulator and ultrasound, of which the latter is increasingly popular in today's regional anesthesia, are used most regularly. Among the target nervous structures, the brachial plexus and the sciatic nerve are most frequently used. Several techniques are described to effectively find and block these nervous structures, *e.g.,* interscalene, supraclavicular, infraclavicular, axillary and humeral blocks for the brachial plexus, and transgluteal, subgluteal, midgluteal and popliteal blocks for the sciatic nerve.

Two of the above-mentioned techniques, infraclavicular brachial plexus and subgluteal sciatic nerve (SNB) blocks are relatively attractive. The infraclavicular brachial plexus block enables application of the local anesthetic agent at a site where all three cords of the plexus are lying close together. Kilka *et al.* described a modification of this technique. The needle is inserted vertically and straight perpendicular to the back, the so-called vertical infraclavicular block (VIB), and the plexus is searched for by electrical nerve stimulation.[12] It provides a very rapid and complete neural blockade, and long-lasting postoperative analgesia.[13] However, the success rate of VIB highly depends on the optimal stimulation of the posterior or medial cord.[14,15] Repositioning of the needle is necessary if no proper stimulation of the posterior or medial cord is obtained. Available algorithms to redirect the needle are all based on personal experience, with a high trial-and-error content. In *chapter 2*, we describe a redirection procedure to reach the posterior or medial cord, which has specifically been tested and verified in clinical practice.

Another attractive approach is the subgluteal ultrasound-guided sciatic nerve block. Being the largest nerve in the human body, surprisingly, sciatic nerve block is still considered as one of the more difficult nerve blocks.[16] The identification of this nerve is sometimes challenging due to its depth and concealment between bony and muscular structures. Therefore, direct visualization with ultrasound may be of help to more accurately find and to more reliably block the nerves. Easy and reliable internal ultrasound landmarks would be helpful for localization of the sciatic nerve. A number of soft tissue landmarks adjacent to nervous structures are increasingly used for nerve identification.[17,18] We describe in *chapter 3* that in the subgluteal region, the sciatic nerve can be located easily (and fast) by using a consistent and reliable soft tissue landmark. This was verified in an anatomic and volunteer study.

Since ultrasound-guided nerve blocks are a relatively recent development, not all clinicians have the same level of experience in handling this technique. Therefore, many workshops are given on this topic, *e.g.,* by ESRA, ASA, NYSORA, DARA and APU Europe, which all use cadavers to explain the difficult 3-dimensional configuration and topography of nervous structures. Comparable cross-sections, however, provided in exactly the same planes as the ultrasound images can not be provided by these means. For that reason, in *chapters 4 and 5*, we provide an overview of the major block sites in arm and leg, in which ultrasound, cross-sectional anatomy, and histology provided by crymicrotomy are matched.

Unfortunately, identification and blockade of the nervous structures is associated with a small risk of potentially devastating nerve damage. Depending on the location of the nerve or plexus, the risk of neuropathy is estimated to be less than 3% for the upper extremity blocks and less than 0.3% for the lower extremity blocks.[19] In the majority of cases, however, the damage is temporary. It may last for weeks and sometimes several months, but permanent nerve damage is seldomly seen.[20]

To minimize this risk, all potential factors that would increase the possibility of injury have to be identified and, if possible, avoided. A number of patient-related factors are identified, among others, obesity, neurologic and metabolic diseases.[21-23] Clinical evidence suggests that patients with pre-existing peripheral nerve injury are more likely to sustain further nerve damage if a second (sub)clinical injury occurs.[24,25] The presence of one or more of these factors could increase the risk of neuropathy, irrespective of the location of the nerve block. In addition, procedure-related factors may increase the risk of nerve damage.

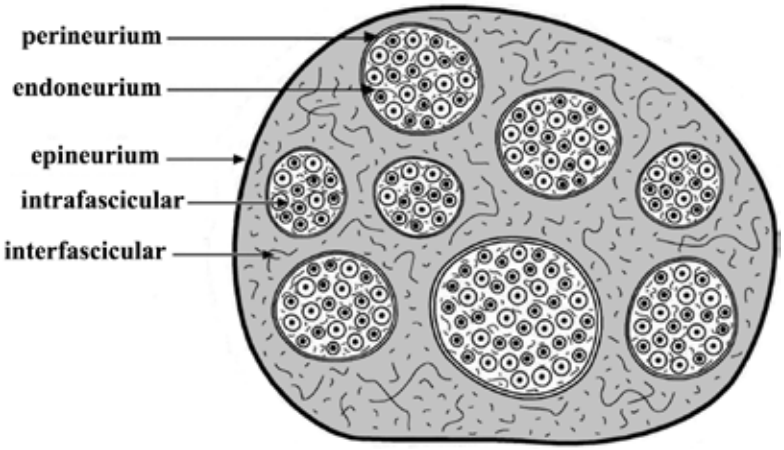

Figure 1. Cross-sectional overview of peripheral nerve.

These include injection pressure, injection side, type of needle, amount and concentration of local anesthetic, toxicity, manipulation of nervous tissue, and high-risk surgery.[26-28]

Although considerable debate still exists, some experts believe that intraneural injection may also be an important factor in the development of neurological sequelae.[29] In case reports, the possible association between intraneural injection and nerve injury is addressed.[30,31] The debate takes another dimension as more studies become available about the relation between intraneural injection of local anesthetics, high injection pressure and nerve damage.[32-38] However, there is no study that summarizes all experimental and clinical data. Therefore, to objectively assess this relation, we performed a systematic review (*chapter 6*). The primary aim of the review is to answer the question whether intraneural injection of local anesthetics, defined as injection inside the perineurium of the nerve (*i.e.,* intrafascicular) or inside the epineurium, but outside the perineurium (*i.e.,* interfascicular, Figure 1) affects the risk of developing nerve damage. In addition, does high injection pressure, high concentration and amount of the injected local anesthetic change the risk of nerve damage?

After determining the severity of the risk of nerve damage after intraneural injection, the next relevant question is to find an explanation of the observed findings. Apart from the etiology, in a meta-analysis, Brull *et al.* found significant difference in the risk of neuropathy between proximal and distal blocks.[19] The rate of occurrence of neuropathy was almost twice as high in the proximal brachial plexus (interscalene) blocks compared to the distal brachial plexus (axillary) blocks.[19] For the sciatic nerve, a similar trend in distribution of risk was reported between proximal and distal. One of the factors that could explain these differences might be related to the nervous structures themselves. Particularly, it would be helpful if differences in internal architecture would exist between proximal and distal parts of the nerves. In *chapters 7 and 8*, the question is answered whether the amount and the distribution of neural and nonneural tissue both inside and outside the nerve correlates with the distribution of the risk of nerve damage.

We determined the ratio of neural to nonneural tissue in situ within the brachial plexus and the sciatic nerve in all major nerve block areas in the upper and lower extremities. Cryomicrotomy is used as it is regarded as the gold standard to obtain undisturbed, high-resolution, cross-sectional images. Conventional imaging modalities such as computer

tomography or magnetic resonance imaging are also helpful to examine undisturbed anatomy. However, limited resolution and technical aspects such as partial volume effect (*i.e.,* pixel representing more than one kind of tissue type by averaging) interfere with their practical implementation.[39,40]

Finally, after establishing the severity of the risk of neuropathy after intraneural injection and the possible anatomic explanation for that, the next step involves the prevention of intraneural injection by early and reliable detection. Therefore, two frequently used tools are applied to assess the location of the needle tip in relation to the nerve, *i.e.,* nerve stimulator and ultrasound. With respect to the nerve stimulator, stimulation thresholds less than 0.5 mA have been recognized to deliver adequate stimulus to trigger a motor response while causing minimal discomfort to the patient.[41,42] However, stimulating currents in the range between 0.2 and 0.5 mA do not guarantee the proximity of the needle to the neural tissue.[43] Furthermore, animal studies have shown that in some cases with the needle intraneurally, a stimulation current higher than 0.5 mA was required to induce a contraction.[44,45] Unfortunately, reliable data from reports on humans are still lacking. Therefore, we conducted a study to determine the minimally required stimulation threshold to elicit a motor response, outside and inside the most superficial part of the brachial plexus during high-resolution, ultrasound-guided, supraclavicular block (*chapter 9*).

For the second tool, ultrasonography, it has been proposed that it adequately captures intraneural injection on macroscopically exposed nerves.[44] However, adequate visualization of nervous structures is not always possible in all patients.[46] A set of visual parameters to detect intraneural injection have been proposed, which could aid the clinician to distinguish between intraneural and extraneural injection.[31,32,47-50] These characteristics are relevant indicators for intraneural injection, but their separate accuracy has not been investigated yet, especially since they are described in studies in which relatively large volumina of local anesthetics were used (5 – 40 ml). Since even very small amounts of local anesthetic have been suggested to cause injury to nerve fascicles,[34,36,50] it would be highly relevant to determine the accuracy of ultrasound to detect intraneural injection after injection of this small amount of local anesthetics as an early sign of intraneural injection. We describe the results of this study in *chapter 10*.

In conclusion, this thesis deals with techniques to more reliably identify nervous structures and subsequently prevent intraneural injection in the practice of regional anesthesia. To identify nerves of the brachial plexus and sciatic nerve, both conventional techniques such as nerve stimulation, as well as ultrasound are described. The first chapters (*2 – 5*), deal with nerve identification techniques using nerve stimulation and ultrasound. The following chapters (*6 – 10*) concern identification and prevention of intraneural needle tip placement and outcome after intraneural injection in the practice of regional anesthesia.

The aim of the individual chapters can be summarized as follows: in *chapter 2*, we provide a redirection protocol for the vertical infraclavicular block to effectively block all cords of the brachial plexus. *Chapter 3* describes the identification of the infragluteal sciatic nerve using consistently visible and easy identifiable tendinous fibers in the proximal long head of biceps femoris. In *chapter 4 and 5*, an extensive overview is given about the sonoanatomy of the brachial plexus and the sciatic nerve. In these reviews, imaging modalities such as anatomy, histology and ultrasonography are optimally matched. In *chapter 6*, we conducted a systematic review of the relation between intraneural injection of local anesthetics and

neurological sequelae. *Chapters 7 and 8* describe the results of an extensive, quantitative analysis of the internal architecture of the brachial plexus and the sciatic nerve. In *chapter 9*, the hypothesis was tested whether nerve stimulation is reliable to distinguish between intraneural and extraneural environment in supraclavicular ultrasound-guided brachial plexus block. In *chapter 10*, we investigated the accuracy of ultrasound to detect intraneural injection after injection of small amount of dye in both brachial plexus and sciatic nerve blocks. Finally, in *chapter 11*, the findings of the studies presented in this thesis are discussed in light of the available data and some recommendations are given for future investigations.

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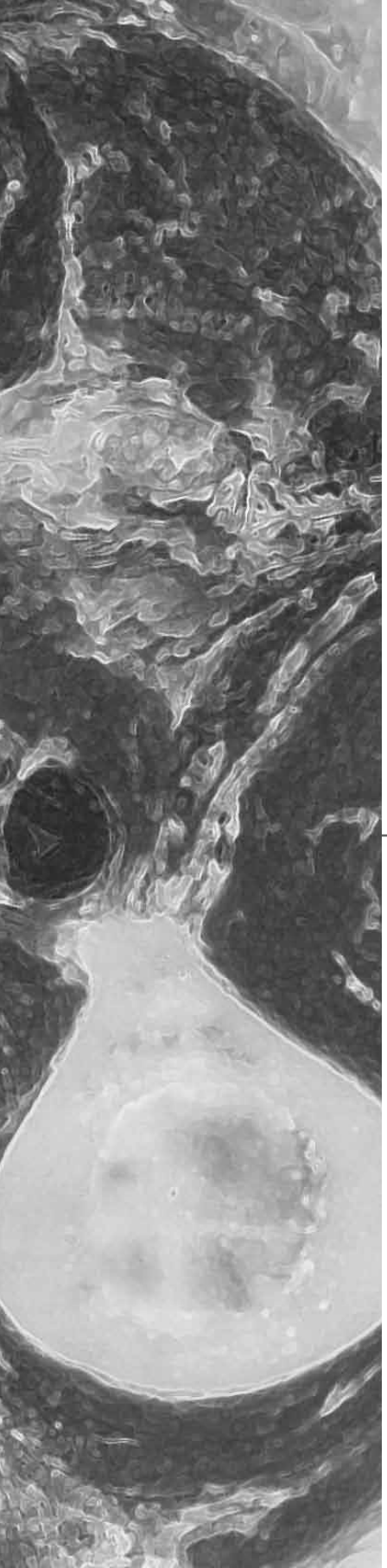

Chapter 2

Vertical Infraclavicular Brachial Plexus Block: Needle Redirection after Elicitation of Elbow Flexion

Nizar Moayeri, Steven Renes, Geert-Jan van Geffen, Gerbrand J. Groen

Regional Anesthesia Pain Medicine 2009; 34: 236-41

Abstract

Background **In vertical infraclavicular block, success depends on proper distal flexion response (medial cord-type) or extension response (posterior cord-type) of the fingers or wrist. Initially, elbow flexion (lateral cord-type) is generally observed. However, specific knowledge about how to reach the medial or posterior cord is lacking. We investigated the mid-infraclavicular area in undisturbed anatomy and tested the findings in a clinical setting.**

Methods **Along a length of 35 mm around the mid-infraclavicular point, cryomicrotomy sections were used to determine the mutual topography of the cords in relation to the axillary artery. Based upon the findings, the anesthesiologists were instructed on how to elicit a distal motor response once a lateral cord-type response was observed in single-shot, Doppler-aided, vertical infraclavicular blocks.**

Results **In the mid-infraclavicular area, the lateral cord always lay anterior to the posterior or medial cord and cranial to the axillary artery; the posterior cord was always cranial to the medial cord, both cords were always located dorsal to the artery. In the clinical study, in 49/50 (98%) of the included patients, distal flexion or extension was elicited as predicted. The overall success rate was 92%. No vascular or lung puncture occurred.**

Conclusions **In the clinical study, in 98% of cases the final stimulation response of posterior or medial cord-type was found as predicted by the findings of the anatomical study. Once lateral cord stimulation is elicited, a further (i.e. deeper) advancement of the needle will result in the proper distal motor response. A redirection algorithm is proposed.**

The vertical infraclavicular block (VIB) has been suggested to provide a very rapid onset of complete neural blockade and long-lasting postoperative analgesia.[1] As first described by Kilka *et al.*, the needle is inserted in the mid-infraclavicular point, vertically and perpendicular to the back and inferior to the clavicle.[2] This region is very attractive to apply the local anesthetic agent since all three cords of the plexus are lying close together. The needle position relative to the lateral, medial or posterior cord is routinely inferred from elicited motor responses.[3] A satisfactory needle position is assumed when electrical stimulation elicits a distal flexor response associated with stimulation of the medial cord (median or ulnar nerve) or a distal extensor response associated with stimulation of the posterior cord (radial nerve).[4]

Reinsertion or repositioning of the needle is necessary if no proper stimulation of the posterior or medial cord is obtained. Suggestions for redirection paths of the needle have been published, however, all based upon personal experiences, with a high trial-and-error content. A redirection procedure to reach the posterior or medial cord, which has specifically been tested in the clinical practice, is lacking.

The topography of the cords of the brachial plexus was studied in the mid-infraclavicular area. This was done using cryomicrotomy sections of cadavers with undisturbed anatomy. We sought to answer the question of how to reach the deeper parts of the brachial plexus, *i.e.,* medial or posterior cord, after stimulation of the lateral cord. The aim of the study was to determine a pattern in topographical organization of the three cords that would be consistent enough to be used as guidance in needle redirection. The feasibility of the anatomical findings was then tested in the clinical setting.

Methods

Anatomy

To preserve the original, undisturbed, neurovascular topography of the brachial plexus, cryomicrotomy was used. The cryomicrotome technique we applied, provided high-resolution images which allowed us to analyse the structures in their exact original position and dimensions, without altering the topographical relations.

After Institutional Review Board approval (University Medical Center Utrecht, Utrecht, the Netherlands) five shoulders from four different cadavers (baseline characteristics shown in Table 1) were obtained from the Department of Functional Anatomy of the University Medical Center Utrecht, Utrecht, the Netherlands. The arm of the cadavers was positioned at the lateral side of the body without flexion of the elbow. The shoulders contained the regions between the scalene muscles and the coracoid process. Digitized consecutive cross-sections (interval, 0.078 mm) of the infraclavicular area were obtained in the sagittal plane. An extensive description of the technique is provided elsewhere.[5] Perpendicular reconstructions of the brachial plexus were obtained following its course in the infraclavicular area using Enhanced Multiplanar reformatting Along Curves software (E-MAC Group, Department of Information and Computing Sciences, University of Utrecht, Utrecht, The Netherlands). Via magnification and a rapid sequential display of consecutive images using the Image Sequence Viewer program (Moayeri N, Groen GJ, Utrecht, The Netherlands),[6] the continuity between the individual cords and nerves was visualized, by which manner the structures were identified (Figure 1).

Table 1. Baseline characteristics of the cadavers

Specimen	Age	Gender	Weight (kg)	Height (cm)	BMI
L1; R1	62	female	73	168	25.9
R2	45	female	85	178	26.8
R3	73	male	92	188	26.0
R4	45	female	63	164	23.4

BMI: Body-Mass Index; R: right shoulder specimen; L: left shoulder specimen

To identify the center of the infraclavicular region during this display, we choose the middle of the line between the suprasternal notch and the most ventral part of the acromial apophysis, as described earlier by Kilka *et al.*[2] At this point, a 22G cannulated needle (Abbocath-T 22G x 51 mm IV cannula, Abbott Laboratories, Chicago, IL) was inserted in the vertical plane, perpendicular to the back and just inferior to the clavicle. The needle was removed, the cannula was left *in situ* and the sagittal images containing the cannula formed the mid-infraclavicular point. Since nearly all infraclavicular brachial plexus blocks are performed lateral to this point, all sections between 5 mm medial (i.e. point +5) and 30 mm lateral (i.e. point -30) to the mid-infraclavicular point were analyzed.

In each section, at 5 mm intervals (*i.e.,* at points +5, 0, -5, -10, -15, -20, -25, -30), outlines of the axillary artery and the brachial plexus constituents in the infraclavicular region were drawn. Thus, a total of 40 images were created in which the position of the lateral, medial and posterior cord was recorded relative to one another and to the axillary artery.

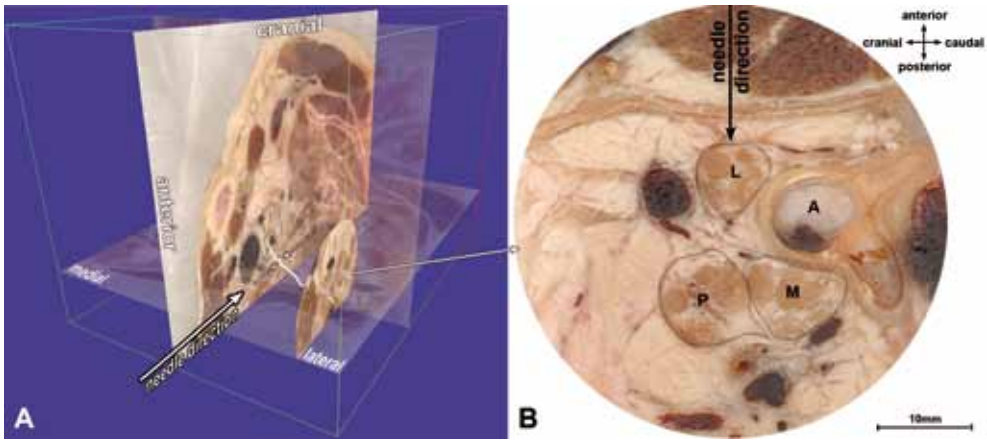

Figure 1. **A.** Reconstructed tissue block highlighting a sagittal cross-section of the shoulder. Reconstructions were made in the trajectory of the white line from 5mm medial to 30mm lateral to the midclavicular point. White small arrows indicate midclavicular point. **B.** Reconstructed image containing the cords of the brachial plexus perpendicular to their axis. Note that the image is rotated (45° clockwise) to an orientation similar as the operator would encounter the patient's position on bed during electrostimulation. *A,* axillary artery; *L,P,M,* lateral, posterior and medial cord.

Clinical setting

Patients

To assess our anatomical findings in the clinical setting, a clinical study was performed in a hospital with an anesthetic department staff familiar with the vertical infraclavicular block. The anesthesiologists performing the blocks were instructed to follow our recommendations for redirecting the needle in the vertical plane. For this purpose, fifty consecutive patients were prospectively recruited, after obtaining institutional review board approval (Bernhoven Hospital, Oss, the Netherlands) and patients' written, informed consent. All patients were scheduled for wrist and/or hand surgery under regional anesthesia and were 17 years or older with American Society of Anesthesiologists physical status 1 to 3. Patients with pre-existing neurological disorders, anatomical abnormalities as a result of bone fractures, allergy to local anesthetics or pregnancy, were ineligible to participate.

Technique

Patients were placed in the supine position with the elbow flexed at 90° and the palm of the hand lying on the abdomen. Patients received a small bolus of midazolam (1-2 mg, intravenous) before beginning with the procedure. A similar dose of midazolam was given, if needed, during surgery. A vertical infraclavicular brachial plexus block using the Doppler approach was performed.[7] In short, a Doppler ultrasound device (Mini Dopplex D900, Huntleigh Healthcare, United Kingdom) was placed under the clavicle at the mid-infraclavicular point parallel to the sagittal plane and perpendicular to the back. Starting from this point, the maximum audible point of the sound of the axillary artery was searched for and designated as the Doppler point. The difference between the Doppler point and the mid-infraclavicular point was recorded. The Doppler point was used as the needle insertion site. A 5 cm insulated needle (Stimuplex D, B. Braun, Melsungen, Germany) connected to a nerve stimulator (HNS 11, B. Braun, Melsungen, Germany) programmed to deliver rectangular direct current impulses with a frequency of 2 Hz, pulse duration 0.1 msec, and intensities of 1.0 mA, was inserted in a strict vertical plane until a visible twitch was observed, which was recorded as first response. The findings of the anatomic pilot study suggested that if the first response was flexion of the elbow, pronation of the forearm, or radial movement of the hand),[3] the needle had to be advanced deeper without angulation until stimulation of either posterior cord (wrist and/or finger extension) or medial cord (finger flexion) was obtained, or the maximum depth of 5 cm was reached. The anesthesiologist had only knowledge of this recommendation. If no initial motor response at all was obtained, the anesthesiologist was free to follow his own experience by inserting the needle more medially after trying a more lateral insertion point. A proper *distal* response was defined as a response of either the posterior (extension of wrist and/or finger) or the medial cord (flexion of fingers) at a stimulation current between 0.15 - 0.50 mA. Lidocaine 1.5% with epinephrine 1:200.000 was injected at a dose of 7 mg/kg after careful aspiration for blood, with a maximum volume of 40 ml, in order to reduce the risk of local anesthetic toxicity.[8]

Block success was defined as complete sensory and motor block in the distribution area of the radial, median, and ulnar nerves at 30 minutes, and assessed by the same anesthesiologist who placed the block. Sensory block was defined as complete anesthesia to pinprick, and tested with a sharp 18 gauge needle in the skin distribution areas of the

median nerve (palmar surface of the thumb and palmar tip of the middle finger), the radial nerve (dorsal side of the wrist) and the ulnar nerve (palmar surface of the fifth finger) at 15 and 30 minutes. Motor block was defined as the inability of the patient to perform the following maneuvers: flexion of the distal interphalangeal joint of the second finger (median nerve), extension of the wrist (radial nerve) and abduction of the third and fourth fingers (ulnar nerve). In addition, failure of the block was considered if more than 100 μg fentanyl was required during surgery. Any accidental puncture of vessels (aspiration of blood) or lung (aspiration of air or decrease of saturation on pulse-oxymeter) was noted.

Data are presented as mean ± standard deviation and range. Analysis of the difference between the Doppler point and the mid-infraclavicular point was done using a two-sided *t*-test. A *P*-value of 0.05 or less was considered statistically significant.

Results

Anatomy

The location of the cords relative to one another showed a consistent pattern: the *lateral cord* lies directly anterior to either the posterior or the medial cord; the *posterior cord* lies directly posterior or posterocranial to the lateral cord, and the *medial cord* lies directly caudal to the posterior cord. Figure 2 illustrates the schematic representation of the mutual topography of the cords as well as their position relative to the axillary artery in the mid-infraclavicular region. This pattern remained the same towards the lateral extent of the area analyzed, with the cords remaining parallel to the axillary artery as it traversed inferiorly toward the axilla. In this trajectory, in all specimens the cords surrounded the axillary artery in a consistent manner: the *lateral cord* lies directly cranial to the artery; the *posterior cord* lies cranial or posterocranial to the artery; and the *medial cord* lies posterior or posterocranial to the artery. The medial cord was not observed caudal to the artery. The axillary artery gradually declined towards lateral, implying that a more lateral insertion also necessitates a more caudal insertion. In the analysed trajectory, on average, the axillary artery descended 9.5 ± 5.0 mm (range 3.5 – 15.2 mm). Finally, the mean diameter in cranio-caudal direction was 5.4 ± 1.4 mm for the lateral cord, 7.8 ± 1.6 mm for the posterior cord, and 6.8 ± 2.0 mm for the medial cord.

In the mid-infraclavicular area, based upon these findings, we predicted that after initial proximal stimulation response of the lateral cord, the proper distal response of posterior or medial cord would be found by advancing the vertically inserted needle deeper (i.e. more dorsal) without deviating from its original vertical course. If no initial lateral cord stimulation was found, a more caudal, vertical re-insertion of the needle with steps of 5mm increments would be sufficient to elicit an elbow flexion response. The findings were used as guidance in the clinical setting.

Clinical study

The baseline characteristics of the fifty consecutive patients are shown in table 2. After insertion of the needle, the first stimulation response was flexion of the elbow in 96% (n=48), extension of the elbow in one patient (2%), and distal flexion of ulnar nerve-type in one patient (2%). After the initial above-mentioned proximal responses, deeper (*i.e.,* more dorsal) advancement of the needle in the sagittal plane without angulation resulted

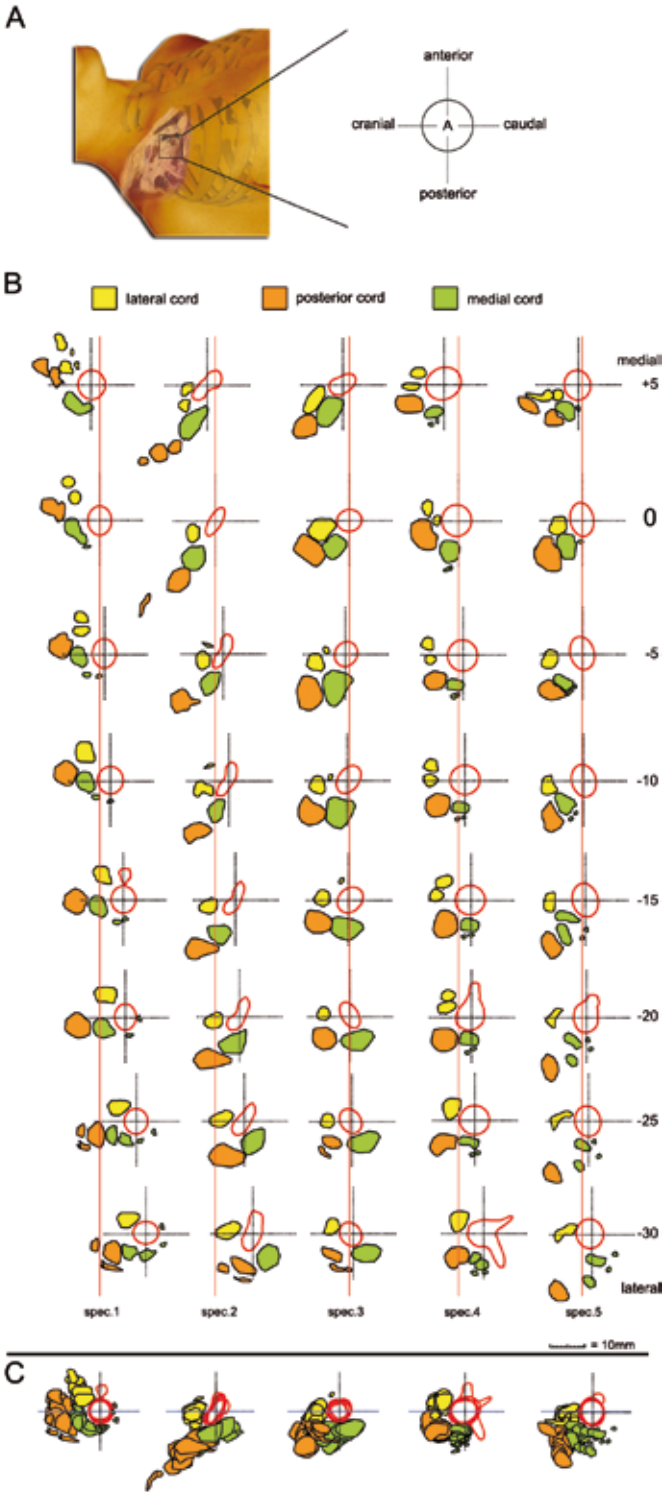

Figure 2. **A.** The figure shows the orientation of the investigated area around the axillary artery (A). **B.** Schematic sagittal representation of the cords and axillary artery from 5mm medial (+5mm) to 30mm lateral (-30mm) in the five specimens (spec.1-5). Vertical red line is centered through the middle of the axillary artery in the mid-infraclavicular point (0 mm). **C.** All neurovascular structures are projected on top of each other, centered around the axillary artery.

Table 2. Baseline characteristics of patients

	All patients (N=50)
Age (yr)	52 ± 13 years (17 - 80)
Height (cm)	171 ± 8 (154 - 187)
Weight (kg)	80 ± 17 (59 - 170)
BMI (kg/m2)	27 ± 6 (20 - 56) †
Final stimulating current (mA)	0.31 ± 0.05 (0.18 - 0.42)
Needle depth to elicit a distal response (mm)	40.5 ± 6.5 (26 - 50) †
Difference between MP and DP (mm)	3.5 (95% CI 1.9 - 5.2 mm) ‡

Data presented as mean ± SD (range). BMI: Body-Mass Index; MP: mid-infraclavicular point; DP: Doppler point; †: relation between BMI and maximum needle depth to elicit a distal response, $p < .0002$ (Pearson correlation test); ‡: $p < .0001$

Table 3. Distribution of patients with initial and final stimulation responses and surgical block success rates after 30 minutes

	Final stimulation response		
Initial stimulation response	Distal: flexion of fingers	Distal: extension of fingers/wrist	Total
Proximal: flexion elbow; N (%) Surgical block success rate; N (%)	37/50 (74%) 35/37 (95%)†	11/50 (22%) 10/11 (91%)†	
Proximal: extension elbow; N (%) Surgical block success rate; N (%)	- -	1/50 (2%) 0/1 (0%)‡	
Distal: flexion of fingers; N (%) Surgical block success rate; N (%)	1/50 (2%) 1/1 (100%)	- -	
Total; N (%) Overall surgical block success; N (%)*	38/50 (76%) 36/38 (95%)†	12/50 (24%) 10/12 (83%)†‡	50/50 (100%) 46/50 (92%)

† Unsuccessful due to incomplete sensory block after 30 minutes
‡ Unsuccessful due to a requirement of greater than 100 µg fentanyl during surgery
* Difference of success rate between distal flexion and/or distal extension is statistically not significant.

in 74% in flexion of the fingers and 24% in extension of the fingers and/or wrist. Thus, the final distal response was seen in 98% (n=49) of patients (table 3). In none of the patients, a more caudal vertical re-insertion was necessary. On average, the needle depth to elicit a distal motor response at a stimulation current between 0.15 and 0.5 mA was 40 ± 7 mm, ranging from 26 to 50 mm. The depth of the needle showed a statistically significant positive correlation with the Body-Mass Index (Pearson correlation test; $p < .0002$).

After 15 minutes, 38% of patients demonstrated total sensory and motor block in the distribution area of the radial, median and ulnar nerves, which increased to 92% after 30 minutes. Within the group of patients with flexion of the fingers as final stimulation, the overall surgical block success rate was 95%, compared to 83% for patients with distal extension as final twitch. In the remaining four patients (8%), the block was considered

a failure, since the palmar surface of the fifth finger was not blocked. Of these, in three patients, complete anesthesia was observed after 45 minutes and they were operated without adjuvant therapy. The remaining patient received general anesthesia. No vascular or lung puncture occurred.

Discussion

The consistent topographical pattern of the cords around the mid-infraclavicular area implies that, if the posterior cord is located dorsal to the lateral cord, the medial cord lies just caudal to the posterior cord, and if the medial cord lies dorsal to the lateral cord, the posterior cord is always just cranial to the medial cord. As can be observed in the mid-infraclavicular area, the medial cord consistently lies more posterior to than caudal to the axillary artery, in a number of cases even posterocranial to the artery (Figure 2). As a consequence, the medial cord (in frontal section) is not located medial to the axillary artery, albeit the name of the cord would suggest a medial position relative to the axillary artery. However, this position is only reached further lateral, adjacent to our investigated area.[9,10]

An optimal distal stimulation response does not necessarily guarantee a successful block in all cases. We found a success rate of 92%, reflecting a similar to higher success rate reported by other authors using vertical infraclavicular technique.[2,4,7,11,12] In our study, the desired stimulation response was defined as distal flexion or extension response. In contrast to this, large case series have shown that a radial-type response yields a higher success rate than median- or ulnar-type response.[13,14] However, the conclusions of these studies are not applicable to more proximal VIB and vice versa, mainly due to the fact that a lateral (pericoracoid) approach to infraclavicular blockade implies a difference in cord topography.

Our suggestions on how to reach the deeper parts of the brachial plexus may be easily implemented in the clinical practice since no deviation from the original needle trajectory is necessary. We also suggest a vertical re-insertion more caudal with steps of 5 mm increments if no initial motor response is found. Small deviations in any direction, which might occur unnoticeably, will result in relatively large displacements of the needle tip.[15] We propose an easy and intuitive rule (the so-called 5-1-1 rule), which just slightly overestimates the amount of deviation: with a 5 cm needle, angulation of 1 degree deviates the needle tip with 1 mm at 5 cm depth. This implies that, for example, angulating a needle with 10 degrees (less than 2 minutes in an analogue clock) displaces the needle tip about 10 mm at 5 cm depth. In our specimens, the cord sizes in the mid-infraclavicular area varied between approximately 5 and 8 mm (uncorrected for tissue shrinkage). We speculate that even rather small angulations of the needle may result in bypassing one of the cords.

The variability in brachial plexus anatomy is generally considered as high. The most important limitation of our study is the small number of the investigated specimens. However, we did find a consistent pattern in the topography of the cords. Despite the assumed high anatomical variability, a much lower variability of motor responses was seen at the investigated location. In this respect, we believe that the clinically relevant variability is not as high as commonly assumed. This could be explained by anatomical observations. First, we have defined the distal motor response as response from either extension of wrist and/or fingers, or flexion of the fingers. This latter definition is slightly different from criteria used by other studies, which include flexion of the wrist in their definition of distal motor response as well. This is an important difference since the median nerve is known to

have dual-cord contribution from the lateral and medial cords. Analysis of classic studies of fiber topography of the median nerve by Sunderland identify pronator teres and flexor carpi radialis fibers in the lateral root, and nerves to the flexor digitorum profundus, flexor pollicis longus, and intrinsic thenar muscles in the medial root.[16] Nerve-injury studies also suggest that median nerve fibers to the finger flexors are most likely found in the medial cord and medial root of the median nerve.[17] With the most common plexus anatomy, one can conclude that flexion of the fingers including the thumb most likely identifies medial cord or medial root to the median nerve stimulation, but wrist flexion may result from either medial or lateral cord stimulation or stimulation to the medial or lateral median nerve roots.[18] Second, a reanalysis of the work of Kerr who gave an extensive anatomic analysis of 175 brachial plexuses,[19] showed in keeping with Hollinshead,[20] a genuine anatomical variability in only 11 of the 175 described cases (6%). The contribution of the inferior trunk or C8 to the lateral cord was seen in only 5 cases. In this respect only the exchange of nerve fibres from the medial (C8,T1) to the lateral (C5-7) cord are important, since it could affect stimulation responses. These anatomic variations, could explain the incompleteness of the block, as seen in 8% of cases in our study, even when a distal stimulation response was observed. Knowledge of the neuroanatomy of this site and more sophisticated analysis of the type of motor stimulation elicited should therefore remain the basic for improving infraclavicular techniques using electrostimulation.

In conclusion, in the mid-infraclavicular area, we found a very consistent pattern in the mutual topographical relation of the three cords of the brachial plexus. Our findings indicated a deeper advancement of the needle without deviation of its original course to obtain proper distal motor responses, once a proximal response of lateral cord-type response is seen. This finding was tested in a clinical setting, where distal motor responses of posterior or medial cord stimulation were obtained in 98% of cases as predicted. The block success rate was 92% without occurrence of any complication.

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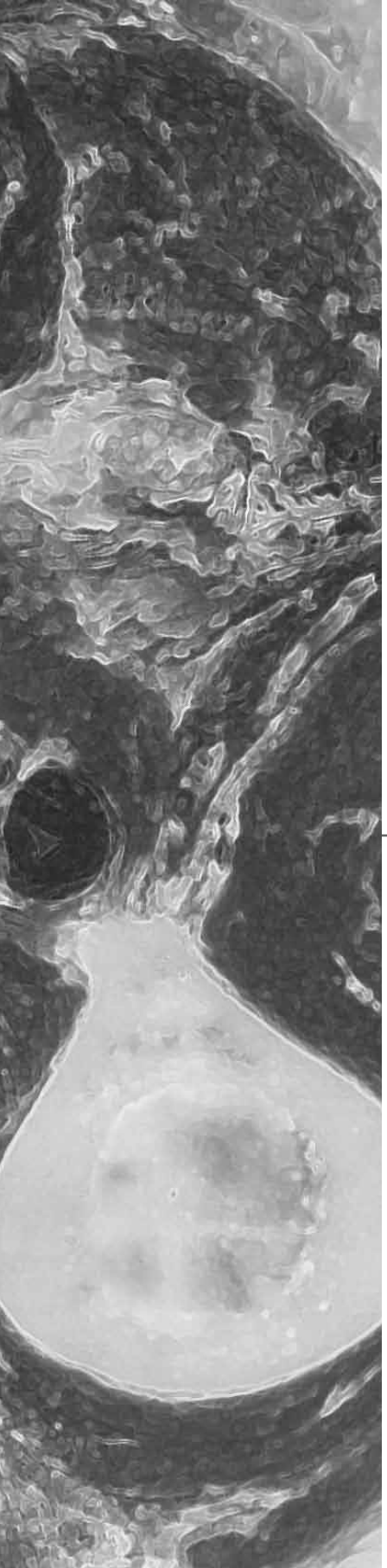

Chapter 3

Soft Tissue Landmark for Ultrasound Identification of the Sciatic Nerve in the Infragluteal Region: the Tendon of the Long Head of the Biceps Femoris Muscle

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Abstract

Background **The sciatic nerve block represents one of the more difficult ultrasound-guided nerve blocks. Easy and reliable internal ultrasound landmarks would be helpful for localization of the sciatic nerve. Earlier, during ultrasound-guided posterior approaches to the infragluteal sciatic nerve, the authors recognized a hyperechoic structure at the medial border of the long head of biceps femoris muscle (BFL). The present study was performed to determine whether this is a potential internal landmark to identify the infragluteal sciatic nerve.**

Methods **The depth and the thickness of this hyperechoic structure, its relationship with the sciatic nerve and the ultrasound visibility of both were recorded in the proximal upper leg of 21 adult volunteers using a linear ultrasound probe in the range of 7 – 13 MHz. The findings were verified by an anatomical study in two cadavers.**

Results **The hyperechoic structure at the medial border of the BFL extended in a dorsoventral direction between 1.4 ± 0.6 cm (mean ± SD) and 2.8 ± 0.8 cm deep from the surface, with a width of 2.2 ± 0.9 mm. Between 2.6 ± 0.9 and 10.0 ± 1.5 cm distal to the subgluteal fold, the sciatic nerve was consistently identified directly at the ventral end of the hyperechoic structure in all volunteers. The anatomical study revealed that this hyperechoic structure corresponds to tendinous fibres inside and at the medial border of the BFL.**

Conclusion **The hyperechoic BFL tendon might be a reliable soft tissue landmark for ultrasound localization of the infragluteal sciatic nerve.**

The sciatic nerve has the largest cross-sectional diameter of the nerves within the human body, but the sciatic nerve block is still considered as one of the more difficult ultrasound-guided nerve blocks.[1] In contrast to the quite superficially located femoral nerve, the sciatic nerve lies more distant from the surface. Increasing depth is related to lower ultrasound resolution.[2] Another important problem in identifying the sciatic nerve with ultrasound so far has been the lack of readily identifiable structures in close relationship with the sciatic nerve. Most ultrasound-guided blocks depend on easily identifiable landmarks, *e.g.* the femoral artery for the femoral nerve or the subclavian artery for the supraclavicular brachial plexus.

Recently, in the midfemoral region, soft tissue landmarks adjacent to the sciatic nerve were used as identification.[3] Barrington and colleagues could reliably identify the sciatic nerve in 95% of patients using ultrasound combined with nerve stimulation. However, the sciatic nerve was identified in only 62.5% of patients when only ultrasound was used. In a previous study,[4] we observed that the sciatic nerve was located at the very end of an infragluteal hyperechoic structure near the proximal attachment of the long head of the biceps femoris muscle (BFL).

We hypothesize that this hyperechoic structure may be a consistent finding, and an easy and reliable soft tissue landmark for the localization of the sciatic nerve in the infragluteal region.

Materials and methods

Patients

After institutional review board approval (Radboud University Medical Center, Nijmegen, the Netherlands) and written informed consent, 21 healthy volunteers (13 males, 8 females, American Society of Anesthesiologists physical status I or II, 25 – 57 years old, 165 – 194 cm, 58 – 103 kg, body mass index 20.2 – 29.9 kg/m^2) participated in this study. Exclusion criteria were obesity (body mass index > 30 kg/m^2) and injury to the lower extremity that caused immobility or skin inflammation. The sciatic nerve was scanned using a linear 7 – 13 MHz ultrasound probe and a Sonosite Micromax unit (Sonosite, Bothell, WA) with image-capturing capabilities.

Every participant had their sciatic nerve of the left leg scanned from the posterior side of the thigh in a prone position. At the beginning, the probe was positioned at the border of the vastus lateralis muscle and BFL, just below the subgluteal fold, perpendicular to the main axis of the sciatic nerve in short-axis view. Slowly, the transducer was moved medially, until the BFL hyperechoic structure was observed. Then, the investigator looked for the sciatic nerve and its relationship with the hyperechoic structure. Ultrasonographic visibility of the sciatic nerve at the very ventral end of this dorsoventral structure and ultrasonographic visibility of the hyperechoic structure of the BFL was noted on a three-point scale: 0 = not visible; 1 = can be identified with difficulty; and 2 = clearly visible.

Furthermore, the first and last points at which this structure was observed in direct relationship with the sciatic nerve were marked and their distance to the subgluteal fold was measured. Halfway between these two points, the following assessments were made: the width, the lateral shift and the depth of the dorsal start and ventral end (*i.e.*, the dorsal border of the sciatic nerve) of the hyperechoic structure of the BFL. Also, the distance

between the skin and the centre of the sciatic nerve was measured.

All assessments were carried out by two anaesthesiologists experienced in ultrasound. While one of the investigators (alternating after each patient) performed the ultrasound and the measurements, the other investigator simultaneously evaluated the images captured and confirmed the identification of the sciatic nerve and the measurements, resulting in one measurement per parameter per patient.

Cadaver study

To confirm the ultrasound results, we performed – with institutional review board approval – an anatomy study using cryomicrotomy in two upper legs of two different cadavers provided by the Department of Functional Anatomy of the University Medical Center Utrecht.[5] The legs contained the region between the first sacral body and the epicondyles of the femur. 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 0.078mm) 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, 1800 – 1900 images per upper leg were collected. In each digital data set of the legs, the midgluteal, infragluteal and midfemoral regions were documented. In addition to the anatomical slices, histological sections (Mallory–Cason trichrome staining) were obtained with an interval of 1 cm.

Results

The hyperechoic structure was found at the medial border of the BFL, between 2.6 ± 0.9 and 10.0 ± 1.5 cm (mean ± SD) distal to the subgluteal fold. In this area, it extended in a dorsoventral direction from a mean depth between 1.4 ± 0.6 and 2.8 ± 0.8 cm from the skin, with a mean width of 2.2 ± 0.9 mm. It showed, from dorsal to ventral, a mean lateral shift of 0.9 ± 0.7 cm. In all participants, at the very end of the BFL hyperechoic structure, the sciatic nerve was clearly identified by its characteristic hyperechoic and fascicular appearance. The sciatic nerve had an oval to triangular shape, whereas its centre was localized at a mean depth of 3.1 ± 0.8 cm. In every subject, the highest visibility score, *i.e.* 2, was obtained by each investigator for both the sciatic nerve and the hyperechoic structure (Figures 1A and B).

The tendinous nature of the structure was confirmed by the anatomy as obtained by cryomicrotomy (Figure 2). They clearly show tendinous fibres inside and at the medial border of the BFL (Figures 2A–C) that correspond with the hyperechoic structure observed with ultrasound. Although it may be interpreted as an intermuscular septum between BFL and semitendinosus, the anatomical cross-sections (Figures 2A and B) and histological sections stained for connective tissue (Figure 2C) identify it as tendon and tendinous fibres of the BFL. Furthermore, intramuscular tendinous fibres in both semitendinosus and semimembranosus were identified (Figures 2B and C). These all correspond to hyperechoic structures inside the semitendinosus and semimembranosus muscles observed during the ultrasound scanning procedure (not included in picture in Figure 1).

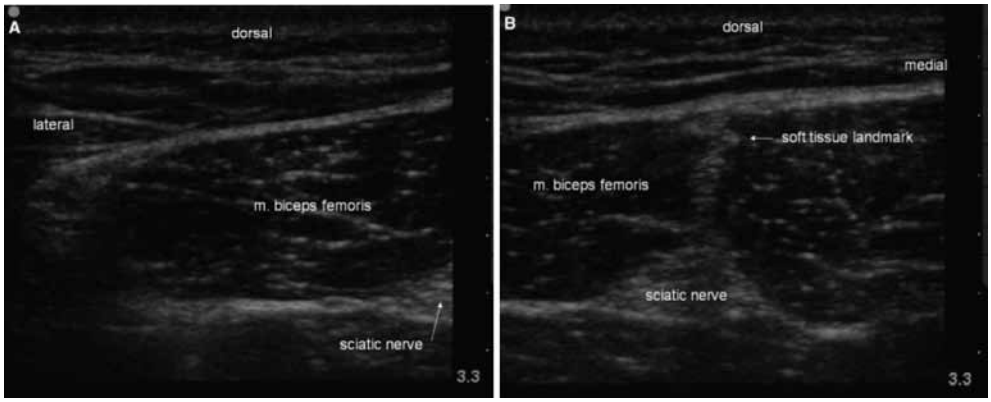

Figure 1. Ultrasound image at the starting point of the scanning procedure, at the lateral border of the biceps femoris muscle (BFL) (A). Further medial scanning reveals, at the medial border of the BFL, the hyperechoic tendinous structure (white arrow) at whose ventral end the sciatic nerve is observed (B).

Discussion

In all volunteers, this hyperechoic structure of the BFL was consistently and reliably identified by ultrasound. It showed a constant relationship with the sciatic nerve, and substantially eases the identification of the sciatic nerve in the infragluteal region with ultrasound.

Systematic scanning was found to be important for a fast identification of the sciatic nerve in this area. The lateral border of the m. biceps femoris should be identified with ultrasound first. It appears as a characteristic half oval on ultrasound (Figure 1A) and can be localized slightly lateral to the posterior midline of the proximal upper leg. After slowly scanning medially, the first dorso-ventral hyperechoic structure that is observed is formed by the tendinous fibres of BFL, showing a slight lateral shift. At the ventral end of this hyperechoic structure, the sciatic nerve can be identified as a generally triangular structure. The intramuscular dorsoventral hyperechoic tendinous structures of semitendinosus and semimembranosus muscles are only observed *after* scanning further medially. They should be ignored.

Meanwhile, this approach became the standard approach in daily clinical practice in our institution for visualizing the sciatic nerve for ultrasoundguided sciatic nerve blocks. We are teaching this approach in workshops for ultrasound-guided regional anaesthesia.

The approach described here can be used in a modified way if one prefers to look first for the sciatic nerve: after having identified the presumed sciatic nerve more distally, e.g. in mid-thigh or in the popliteal fossa, the sciatic nerve can be followed cephalad to the proximal thigh. Finally, just below the subgluteal fold, the hyperechoic BFL tendinous structure should point to the sciatic nerve.

Other approaches to localize the sciatic nerve with ultrasound have been described. Tsui and Finucane suggested localizing the tibial nerve near the popliteal vessels at the popliteal crease and from there scanning proximally ('tracing back') to the common sciatic nerve.[6] A disadvantage of this trace back approach is a limited nerve visibility in the region between the popliteal crease and division/convergence between the tibial nerve and the

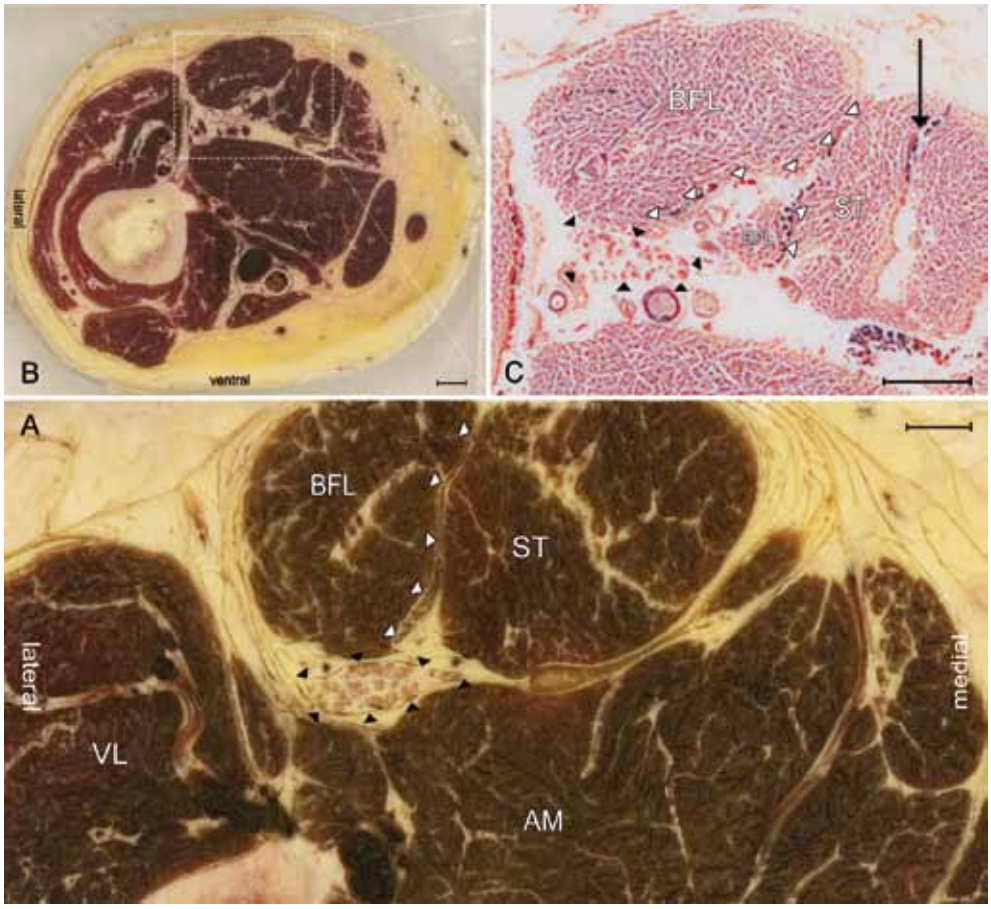

Figure 2. Enlarged cryomicrotome cross-section of the proximal thigh (dorsal side up) showing the tendon at the medial border of the BFL (A). Cryomicrotome cross-section from the second cadaver (B) with an enlarged histological section of the demarcated area at the same level (C). White arrowheads: tendon and tendinous fibres of the BFL corresponding to the hyperechoic structure; black arrowheads: sciatic nerve; black arrow in (C): intramuscular tendinous fibres in the semimembranosus muscle. AM, adductor magnus; BFL, long head of biceps femoris; ST, semitendinosus; VL, vastus lateralis. Scale = 1 cm.

common peroneal nerve[4] and a limited ultrasound visibility of the division/convergence itself between the tibial nerve and the common peroneal nerve,[7–9] which determines the formation of the common sciatic nerve.

Chan *et al.*[1] systematically scanned the sciatic nerve at three locations, i.e. the gluteal, infragluteal and proximal thigh regions in 15 volunteers. With a curved array, low-frequency ultrasound probe in the range of 2 – 5 MHz, ultrasound identification of deep bony landmarks – ischial spine, ischial tuberosity and lesser trochanter – provided a consistent guide to the sciatic nerve at these locations.

Similarly, Karmakar *et al.*[10] localized, with a curved array, low-frequency ultrasound probe in the range of 2 – 5 MHz, the sciatic nerve in the subgluteal space, between the

bony landmarks of greater trochanter and ischial tuberosity. The deep localization in the subgluteal space with a lower ultrasound resolution may make the exact localization of the sciatic nerve difficult. However, identification of the subgluteal space alone seemed to be sufficient for an ultrasound-guided sciatic nerve block. The fact that the subgluteal space approach has a higher chance to concurrently block the posterior femoral cutaneous nerve might be of minor clinical importance. The posterior femoral cutaneous nerve is a pure cutaneous nerve, clinically not relevant for foot surgery or tourniquetinduced pain and, if needed, it can be easily blocked by the surgeon with local skin infiltration.[11] An advantage of proximal sciatic nerve blocks is that they are reliably above the division in the tibial nerve and the common peroneal nerve. As our approach is also a proximal sciatic nerve block, this is also true for our approach.

Recently, Barrington *et al.*[3] also described soft tissue landmarks for ultrasonographic identification of the sciatic nerve, but more distally in the mid-thigh region. They were able to identify the sciatic nerve in 95% of patients when nerve stimulation was applied as well. Plain ultrasound identification of the sciatic nerve was observed in only 62.5%. In contrast, in our study, in the more proximal infragluteal region, the sciatic nerve was reliably identified in all subjects. These differences could be related to regional differences in the ultrasonographic imaging characteristics of the sciatic nerve, but can also be explained by differences between the study subjects. We only studied relatively young, healthy and lean volunteers. The clinical usefulness of our approach in patients with possibly limited ultrasound imaging, as *e.g.* patients with a high body mass index or elderly patients, has to be investigated in the future.

A second limitation is that in our study the ultrasound was only performed in the prone position. For a sciatic nerve block, however, many anaesthesiologists prefer a lateral decubitus positioning with a slight forward tilt and the foot on the side to be blocked over the dependent leg. Whether this position has an influence on the success of the described ultrasound technique also has to be investigated in the future.

A third limitation is that we only visualized the sciatic nerve ultrasonographically without confirmation by another method (*e.g.*, nerve stimulation). However, in all cases the sciatic nerve was concordantly identified by its typical hyperechoic and fascicular appearance by two investigators experienced in ultrasound-guided peripheral nerve block. Omitting the electrical stimulation via a needle with its inherent discomfort and potential damage for the volunteer is in keeping with other studies of the ultrasound appearance of peripheral nerves without using electrical stimulation as a confirmatory signal.[12,13]

In conclusion, the ultrasound approach utilizing the BFL-tendon as an internal landmark might be a valuable tool to the anaesthesiologist for localization of the sciatic nerve in the infragluteal region.

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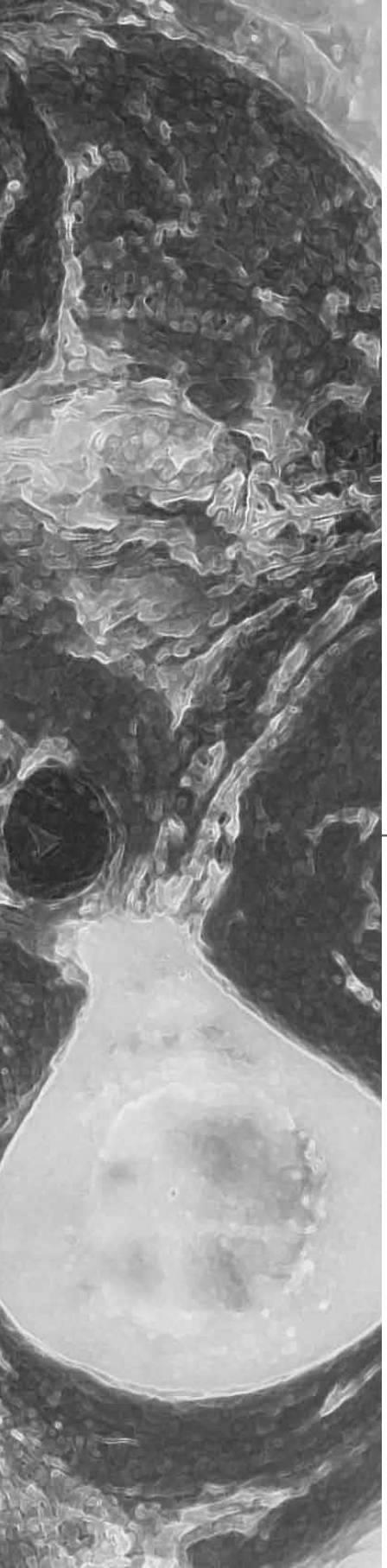

Chapter 4

Correlation between Ultrasound Imaging, Cross-Sectional Anatomy and Histology of the Brachial Plexus: a Review

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Abstract

The anatomy of the brachial plexus is complex. In order to facilitate the understanding of the ultrasound appearance of the brachial plexus, we present a review of important anatomical considerations. A detailed correlation of reconstructed, cross-sectional gross anatomy and histology with ultrasound sonoanatomy is provided.

Sonoanatomy of the brachial plexus is complex, requiring a thorough knowledge of cross-sectional anatomy for identification of nerves, adjacent structures and anatomical variations.[1] In addition to the three commonly planes of imaging, i.e. axial, coronal and sagittal, other viewing planes are often necessary to optimize image quality using a 90 degree angle of insonation to the nerves. Continuous adjustments of pressure, alignment, rotating and tilting manoeuvres are basic to find recognizable patterns of structures and landmarks of the brachial plexuses, however, still-images remain indispensable. This requires anatomical cross-sections in different planes, equivalent to those observed during ultrasonography.

We employed data obtained by cryomicrotomy to calculate the optimal planes for a meticulous comparison of ultrasonography and gross anatomy at the major locations of the brachial plexus blocks. To reliably compare the images of cryomicrotomy and ultrasound, the images have been matched in plane, location and angle. Histology was added as well. Cryomicrotomy was used since it is considered the gold standard of examining undisturbed topography of nerve structures.[2] 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.[3] A major limitation of cryomicrotomy is post-mortem examination of the tissue. This does not take into account the tissue oxygenation, blood circulation, and the elasticity of the structures in vivo.

The recognition of similar patterns in ultrasonography, gross anatomy and histology of the brachial plexus reflects the clinical relevance of this correlative review. This might increase awareness of relevant local anatomy, prevent unnecessary damage and improve success rate of the block.

This review aims to highlight those anatomical aspects of the brachial plexus that are relevant for pattern recognition in ultrasonography. Subsequently, sonoanatomical correlations using gross anatomical specimens and histological sections are presented, particularly with regard to differences between the proximal and distal brachial plexus.

Gross Anatomy of the Brachial Plexus

The brachial plexus is formed by the ventral rami of C5-T1, with variable contributions from C4 and T2. The upper three, C5-7-roots are easy accessible between the anterior and medial scalene muscle. However, the lower roots C8 and T1, are deeply situated, dorsal to the subclavian artery, and therefore more difficult to access.

Between the anterior and middle scalene muscles, the cervical nerve roots descend with varying angulation to unite and form trunks at various distances from their intervertebral foramina (Figure 1). The angles between the brachial plexus nerve roots and the axis of the spinal cord gradually decrease, i.e. the nerve exits at C5 sharply caudal, whereas the angle at T1 is almost straight.[4,5] Optimal ultrasound imaging of individual nerve roots is only provided when the probe angle is varied, perpendicular to each nerve root axis. Thus, it is almost impossible to clearly capture all nerve roots in one image using one angle of the probe. Such a view is only possible when nerves run parallel to each other. This generally occurs more distally in the brachial plexus, starting in the supraclavicular region.

The average distance between the exit of the intervertebral foramen and the point of formation of the trunks varies between 43 mm for C5, 50 mm for C6, 58 mm for C7, 34

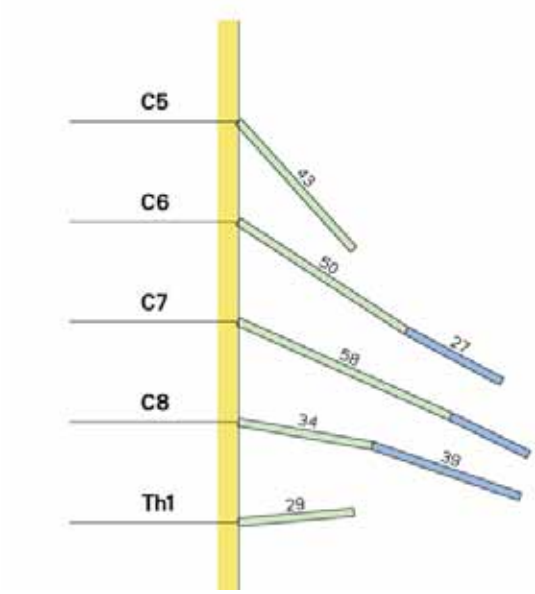

Figure 1: Survey of average angles (degrees) and lengths (mm) of roots and trunks (blue color) after emerging and declining from the spinal cord. The distance between the intervertebral foramina exit and formation of trunks is depicted in green. (Adapted from Bonnel[4])

mm for C8 and 29 mm for T1.[4,6] The length of the upper and lower trunk is variable, *i.e.,* on average 27 and 39 mm, respectively, whereas the upper trunk has a larger diameter than the lower trunk. The clinical impact of these parameters is clear: roots and trunks are not always easy differentiated from each other. In ultrasound-guided interscalene nerve blocks, *e.g.* for shoulder surgery, the needle is aimed at the two most superficial hypoechoic oval nervous structures.[7]

The nerve roots then proceed to the supraclavicular area where they form three trunks. All three trunks separate into anterior (flexor) and posterior (extensor) divisions, on average 65 mm from the vertebral foramina.[4] The divisions are in close proximity to the subclavian artery as they cross the first rib, cephalic and posterior to the subclavian artery. To visualize the supraclavicular brachial plexus the ultrasound transducer is placed in an oblique antero-posterior plane. Consequently, in ultrasound, the position of the brachial plexus relative to the subclavian artery may vary between 'cranio-posterior' (probe in a more sagittal plane) and 'lateral' (probe in more coronal plane). This should be taken into account when performing a supraclavicular brachial plexus block. Whereas, generally, the relative sonoanatomical position of the brachial plexus to the artery is described as 'lateral', one should be aware that depending on the probe position this could also be cranio-posterior.

In the proximal infraclavicular area, the divisions form three cords: the lateral, medial and posterior cords, which are grouped together superior and dorsal to the axillary artery.[8] At the second half of the clavicle the medial cord moves caudal to the axillary artery. Finally it lies between the axillary artery and vein.

Generally at the trajectory between the second half of the clavicle and the lateral border of the pectoralis minor muscle, the three cords give rise to the terminal branches of the brachial plexus in the upper extremity, *i.e.,* the musculocutaneous, median, ulnar, axillary and radial nerves.

Table 1. Fascicle characteristics and echotexture of the proximal and distal brachial plexus.

	Proximal Brachial Plexus	Distal Brachial Plexus
Fascicle size	large	small
Fascicle number	small	large
Fascicle pattern	mono-oligofascicular	multifascicular
Echotexture	hypoechoic (black)	hyperechoic (white)

Micro-Anatomy of the Brachial Plexus

The micro-anatomy of the brachial plexus does not differ substantially from that of peripheral nerves. Both contain fascicles surrounded by epineurial connective tissue. However, the number and size of the nerve fascicles may be different. This difference is largest at the level of the nerve roots. The nerve roots contain few and large fascicles.[4,6,9] In the brachial plexus, from proximal to distal, the number of fascicles increases, whereas the size of the fascicles decreases. Thus, a mono- or oligofascicular pattern is found proximally and a multifascicular pattern more distally.[3-6,9] (Table 1)

Also the relative and absolute amount of the nonneural tissue of the brachial plexus increases from proximal to distal. Whereas the amount of neural tissue remains about the same throughout the brachial plexus, the ratio of neural to nonneural tissue increases from 1:1 in the interscalene and supraclavicular to 1:2 in the midinfraclavicular and subcoracoid regions.[3]

The ultrasound appearance of a peripheral nerve is based upon echogenicity and shape. By high frequency ultrasound (> 10 MHz) the echotexture of peripheral nerves was determined.[10-12] The resolution of the internal topography and internal structural details depends on the surrounding tissues and the depth at which the nerve is visualised. The ability to provide high image resolution in the near field (3 – 4 cm) by high frequency ultrasound (> 10 MHz) is offset by the limited penetration capacity.[13]

On high-resolution sonography, the number and size of individual fascicles depend on the frequency of the applied transducer. Details up to 1 mm are discerned by this method.[10] The fascicle size varies markedly within individual sections, with a cross-sectional area ranging from < 0.001 to 8 mm^2.[9] The largest fascicles are present almost exclusively at the level of the nerve roots of the brachial plexus.[9] Therefore, fascicles with small diameters are missed by ultrasound. In the sciatic nerve, Silvestri *et al.* showed that only about one-third of fascicles is depicted with 15 MHz ultrasound.[10] As an implication, the total amount of neuronal fascicles observed by ultrasound is much lower compared to the actual number observed by light microscopy.

A peripheral nerve shows a mixture of hypoechoic and hyperechoic structures constituting a typical honeycomb structure.[14] Side by side comparison between ultrasound transverse scans of peripheral nerves and their corresponding histological slices demonstrate that the round *hypoechoic* areas seen with ultrasound coincide with *neural tissue*.[15-19] The *hyperechoic* background surrounding the hypoechoic areas correlates with the layers of *connective tissue*.[20]

Because the micro-anatomy of brachial plexus and peripheral nerves show similarities, the typical honeycomb ultrasound appearance is also observed in the brachial plexus.

However, ultrasound imaging of the proximal brachial plexus generally shows hypoechoic ('black') oval and solid structures in the interscalene area, corresponding with the cervical nerve roots.[7]

Equivalent anatomical and histological sections show a denser configuration of the proximal cervical nerves with less connective tissue, indicating an oligofascicular pattern.[3] This is also in keeping with the ultrasonographic observations in the brachial plexus of cadavers.[16]

In our opinion, the similarity in pattern of disperse to more dense in anatomy, histology and ultrasound, as shown from distal to proximal in the brachial plexus, can only be explained by accepting that 'black' in ultrasonography of peripheral nerves is equivalent to nervous tissue. Therefore on ultrasound, a multifascicular pattern displays a black and white speckled (honeycomb) image, whereas an oligofascicular pattern is visualized as a more solid, oval and black structure.

Intraneural injections should be avoided. However, even with ultrasound-guided nerve blocks, accidental intraneural injection cannot be overcome.[21,22] If this occurs in the proximal brachial plexus it might more frequently result in an intrafascicular injection compared to a more distal inadvertent intraneural injection.[3] A further clinical impact is that especially injection inside the hypoechoic nervous structures should be avoided.

Echotexture of the Brachial Plexus

The ultrasound probe position at five anatomical locations along the course of the brachial plexus was described by Perlas *et al.*[23] An axial oblique plane for the interscalene location, a coronal oblique plane for the supraclavicular location, a parasagittal plane for the infraclavicular location, and transverse planes for the axillary, midhumeral and more distal locations. Pressure, alignment, rotating and tilting with the ultrasound transducer is necessary to maximize reflection at nerve/tissue interfaces in order to optimize image quality.

Interscalene area

In the superior interscalene region in an axial oblique cross-section (Figure 2A), the roots of the brachial plexus are interposed between the scalenus anterior and medius muscles (Figure 3A,B). The fifth, sixth and seventh cervical roots can be well visualized by ultrasound as they leave the intervertebral foramina in a downward and outward direction, the C5-root more oblique than the lower ones.[24] Because of their deep location, the C5 and T1 roots are more difficult to visualize by ultrasound, *i.e.,* in 80% (C8) and 59% (T1) of cases.[25] The characteristic sonographic appearance of the brachial plexus is a chain of hypoechoic nodules (Figure 3C, D).[26]

These hypoechoic nodules vary in number from a few to a significant cluster and can be surrounded by relative echogenic surrounding structures, the connective tissue elements.[27] The internal structure of the exiting roots can not be shown by ultrasound.[28] The few adjacent fascicles are coalesced and are seen as one oval shaped hypoechoic structure.[10] Therefore the roots are often seen and depicted as black dots. This fits with the oligofascicular description of the proximal parts of the brachial plexus described earlier.[3-6,9] Histological sectioning further reveals the fascicular pattern of the cervical nerve roots. (Figure 3E,F).

In the inferior interscalene region the roots unite to form the trunks. In the sagittal oblique cross-section through the plexus, they are seen as discrete rounded hypoechoic nodules with some internal fascicular pattern.[28]

On longitudinal scanning each hypoechoic nodule can be visualized as a hypoechoic tubular structure with some internal echogenic fibrillar structures.[29] These echogenic structures can be seen as little white punctuations within and around the "black dots". The average cross-sectional nerve area (the hypoechoic structures) in the superior, middle and inferior trunk was 0.07; 0.09 and 0.09 cm^2 respectively, but the hyperechoic rim, which is believed to represent the epineurial connective tissue surrounding the hypoechoic fascicles was not included.[30] However, there is no direct data supporting the fact that the hyperechoic rim actually represents the epineurial connective tissue. In ultrasound, the outer boundaries of the nerves are usually hard to define because of similarity in hyperechoic appearance of the connective tissue fascial layers that surround the brachial plexus, and the epineurium.

Supraclavicular area

Dorsocranial to the subclavian artery, the trunks start to reorganize in divisions. In 10% of the subjects examined, the inferior trunk is located inferior to the subclavian artery.[31] In a coronal oblique plane ultrasonographic scanning reveals the brachial plexus as a cluster of hypoechoic nodules of varying size that represent the divisions seen on transverse scanning (Figure 2B). The cluster of "grapes" is located cranio-posterior (and lateral) to the subclavian artery, with clear visualization of the underlying first rib and apical pleura (Figure 4A-D).[32-34]

In the longitudinal plane the tubular and fibrillar nature of the divisions was proven.[28] At the supraclavicular level, the emergence of branching increases the number of fascicles and also the quantity of connective tissue in the brachial plexus (Figure 4E, F). Therefore "the cluster of grapes" gets a more speckled ultrasound appearance.

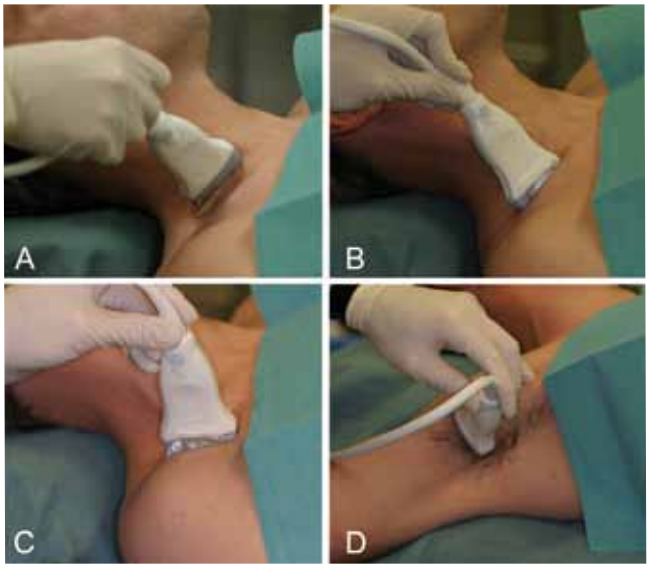

Figure 2. Survey of probe positions in the interscalene (A), supraclavicular (B), infraclavicular (C) and axillary regions (D).

Infraclavicular area

In the infraclavicular region (Figure 2C), beneath the clavicle, the plexus cords are distributed cranial and dorsal to the axillary artery, initially covered by the pectoralis major muscle, but later also by the pectoralis minor muscle (Figure 5A, B). More distally, at the level of the coracoid proces, the cords will reposition themselves medially, laterally and posteriorly around the vessel.[8] Since the plexus is covered by two muscles at a depth of about 4 cm, ultrasound images of this anatomical location will always remain inferior to those of other approaches to the brachial plexus because the interposed muscles absorb the high frequency ultrasound waves.

In the proximal infraclavicular area, the microscopic plexus architecture shows a large number of fascicles of small diameter. This scattered, polyfascicular pattern (Figure 5E,F) provides a more hyperechoic appearance on ultrasound imaging (Figure 5C, D).[35] Close to the artery in the cranioposterior quadrant, the shortest distance to all cords can be found.[36] When performing an ultrasound guided lateral infraclavicular block, a single-injection close to the artery in the cranioposterior quadrant may theoretically give efficient local anesthetic distribution to all cords.[37,38]

Axillary Area

High in the axilla (Figure 2D), around the axillary artery, the terminal branches of the brachial plexus are formed. In almost all cases the musculocutaneous nerve branches early from the lateral cord and courses between the coracobrachialis and biceps muscles. However, a trajectory parallel to the median nerve and lateral to the brachial artery is reported.[39] In the upper arm, the position of the radial nerve may vary between posterolateral and anterolateral to the axillary artery, and that of the median nerve between anteromedial and posteromedial to the artery. In the majority of patients (about 60%) the ulnar nerve is found posteromedial to the artery (Figure 6A, B).[40]

By ultrasonography the musculocutaneous nerve can be easily imaged by moving the probe over the medial bicipital groove toward the level of the pectoralis major grease. The musculocutaneous nerve has a hyperechoic appearance lying in a fascial plane between the coracobrachialis muscle and the biceps muscle (Figure 6C, D).[41,42] Because of the uneven disposition of the adipose tissue, the epineurium presents an oval shape in transverse section. The arrangement of the epineurium may represent the morphological adaptation between the dynamic structure of the coracobrachial muscle and the static musculocutaneous nerve.[43]

On ultrasound imaging in short axis view, the radial, ulnar and median nerve show multiple round or oval hypoechoic areas embedded in a relatively hyperechoic background.[44] The "salt-and-pepper" appearance is due to internal variations in the density of neural tissues within the nerve as described earlier in this article (Figure 6C, D). In longitudinal section the nerves appears as band-like structures with multiple hypoechoic, longitudinal (but discontinuous) lines separated by hyperechoic lines.[45-48]

In conclusion, the differences in internal architecture of the brachial plexus may explain the different ultrasound appearance of the various parts of the brachial plexus. The shown correlations between ultrasound images, cross-sectional anatomy and histology should facilitate identification of anatomical relationships and recognition of brachial plexus variations.

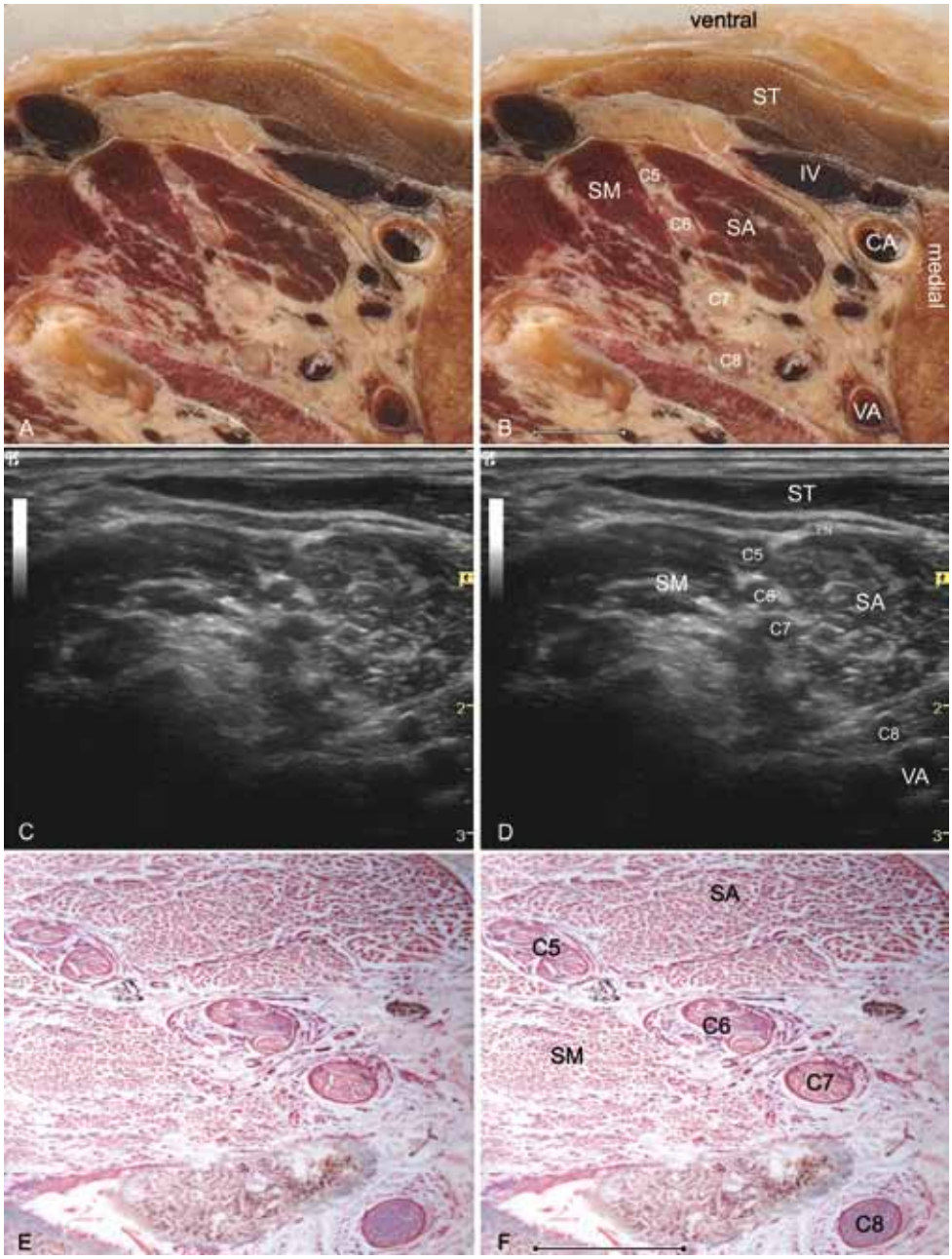

Figure 3. Interscalene region, axial oblique views of the brachial plexus and adjacent structures, left column without labels, right column with labels. (A, B) Reconstructed anatomical views from digitized cryomicrotomy cross-sections; (C, D) ultrasonographic short axis views showing the cervical nerves as hypoechogenic, "black dots"; (E, F) histological section (Mallory-Cason trichrome staining) comparable to interscalene axial oblique view. C5-7 show an oligofascicular pattern, nerve root T1 clearly displays a monofascicular pattern. C5-8, cervical spinal nerves 5-8; CA, common carotid artery; IV, internal jugular vein; PN, phrenic nerve; SA, scalenus anterior muscle; SM, scalenus medius muscle; ST, sternocleidomastoid muscle; VA, vertebral artery. Bar = 1 cm

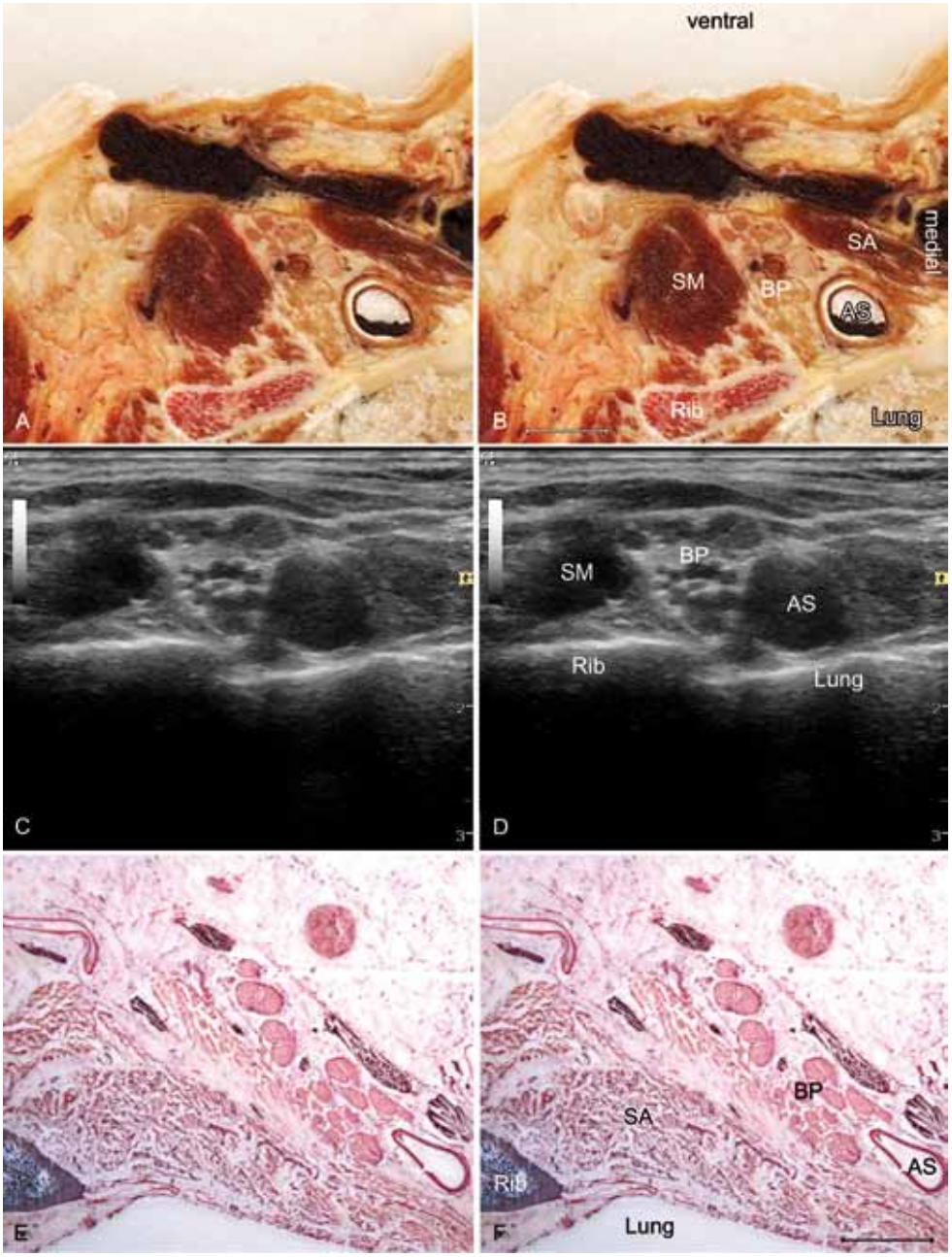

Figure 4. Supraclavicular region. Coronal oblique views of the brachial plexus (BP) and adjacent structures, left column without labels, right column with labels. (A, B) Reconstructed anatomical views from digitized cryomicrotomy cross-sections; (C, D) ultrasonographic short axis views showing the multiple fascicles that generate the "grape-like" structure of the supraclavicular brachial plexus; (E, F) histological section (Mallory-Cason trichrome staining) comparable to supraclavicular coronal oblique view, demonstrating the multifascicular pattern of the supraclavicular brachial plexus. BP, brachial plexus; SA: scalenus anterior muscle; SM: scalenus medius muscle; AS, subclavian artery. Bar = 1 cm

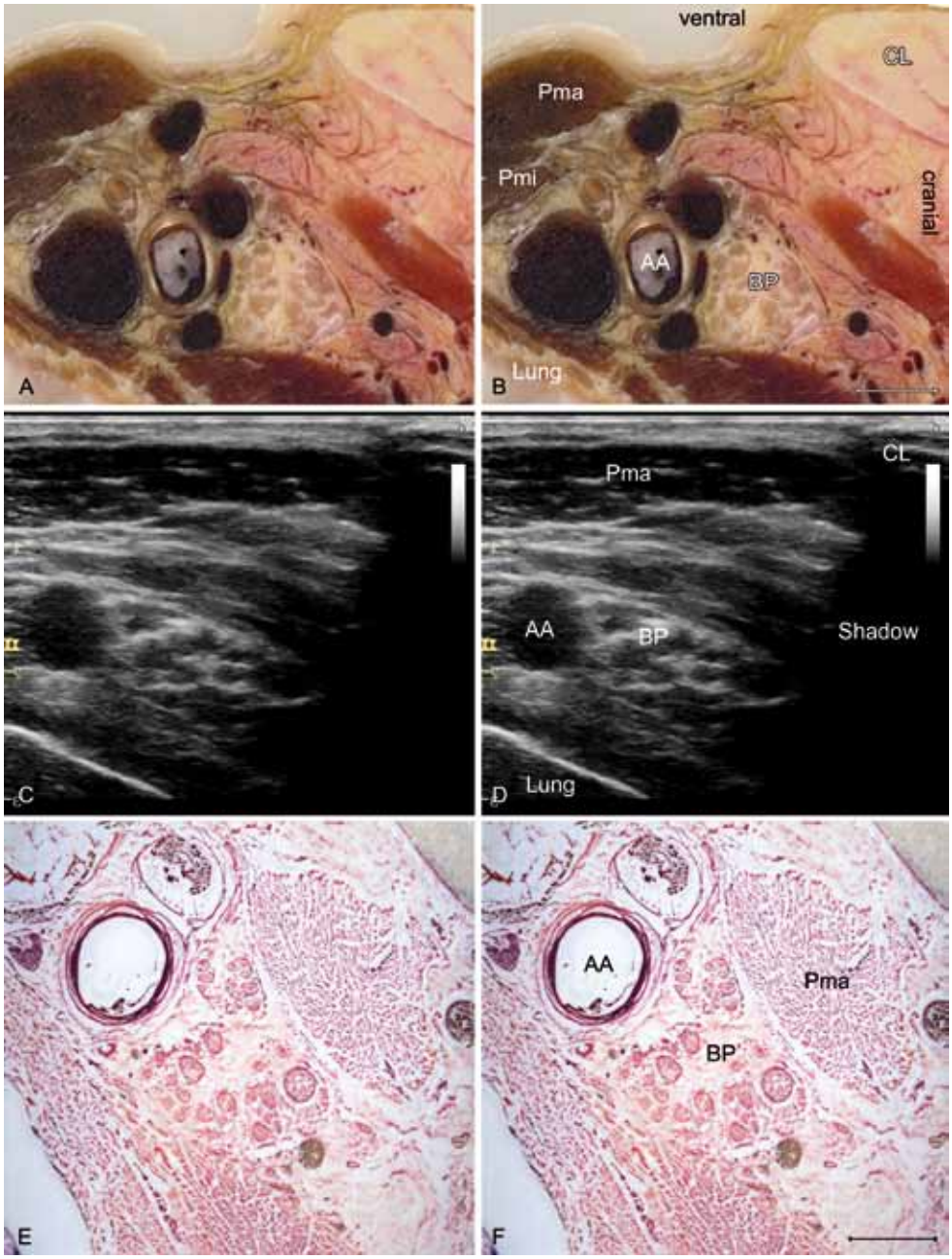

Figure 5. Infraclavicular region. Parasagittal views of the proximal infraclavicular brachial plexus (BP) and adjacent structures, left column without labels, right column with labels. (A, B) Reconstructed anatomical views from digitized cryomicrotomy cross-sections; (C, D) ultrasonographic short axis views; (E, F) histological section (Mallory-Cason trichrome staining) comparable to infraclavicular parasagittal view. The multiple fascicles start to reorganize into the lateral, medial and posterior cord surrounded by loose epineurium. AA, axillary artery; BP, brachial plexus; CL, clavicle with acoustic shadowing; Pma, pectoralis major muscle; Pmi, pectoralis minor muscle; Bar = 1 cm

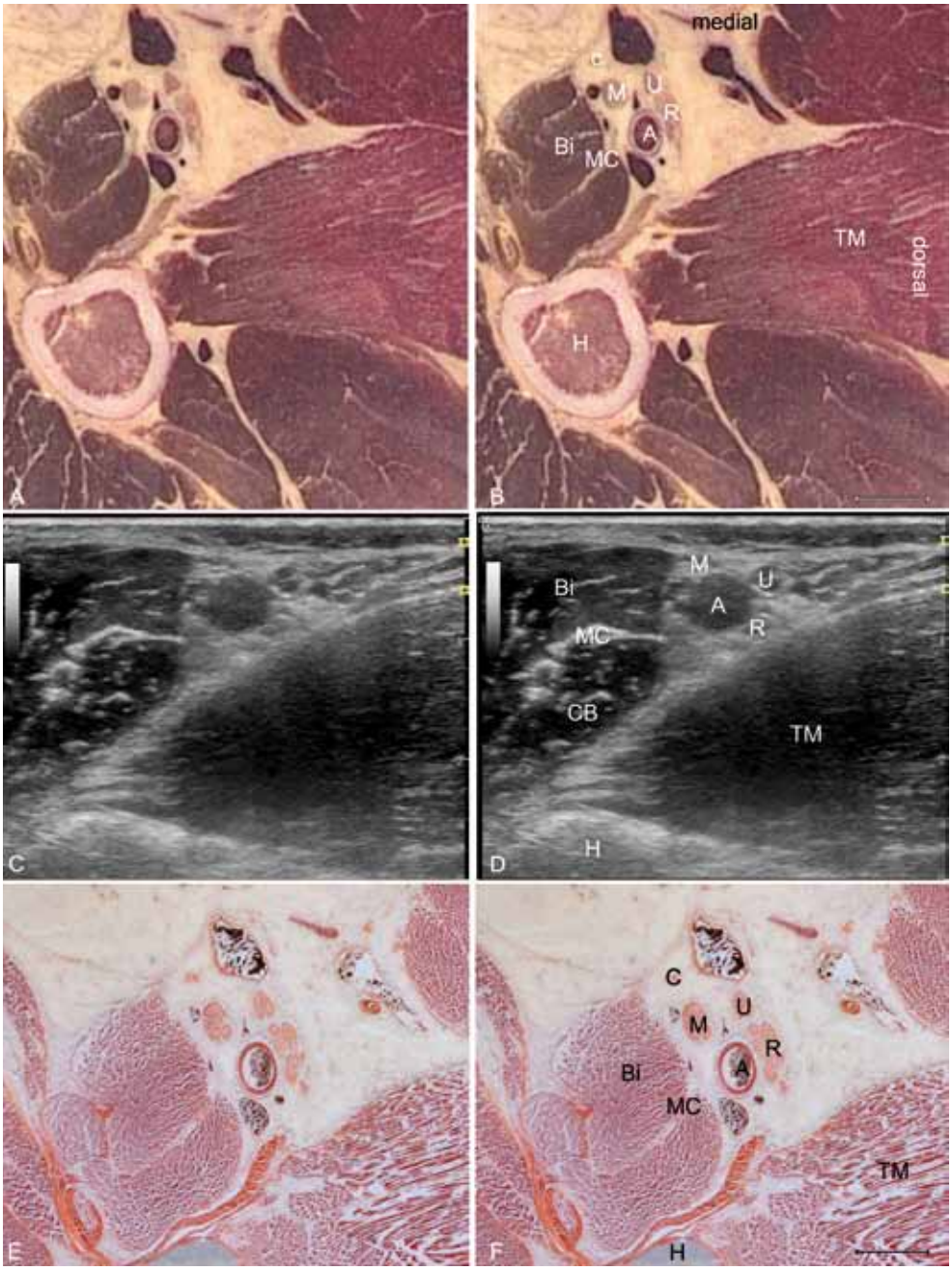

Figure 6. Axillary region. Transverse views of the brachial plexus (BP) and adjacent structures high in the axilla, left column without labels, right column with labels. (A,B) Reconstructed anatomical views from digitized cryomicrotomy cross-sections; (C,D) ultrasonographic short axis views; (E,F) histological section (Mallory-Cason trichrome staining) comparable to axillary transverse view. A, brachial artery; Bi, biceps brachii muscle; C, cutaneous brachial nerve; CB, coracobrachialis muscle; H, humerus; TM, teres major muscle; M, median nerve; MC, musculocutaneus nerve; R, radial nerve; U, ulnar nerve; Bar = 1 cm

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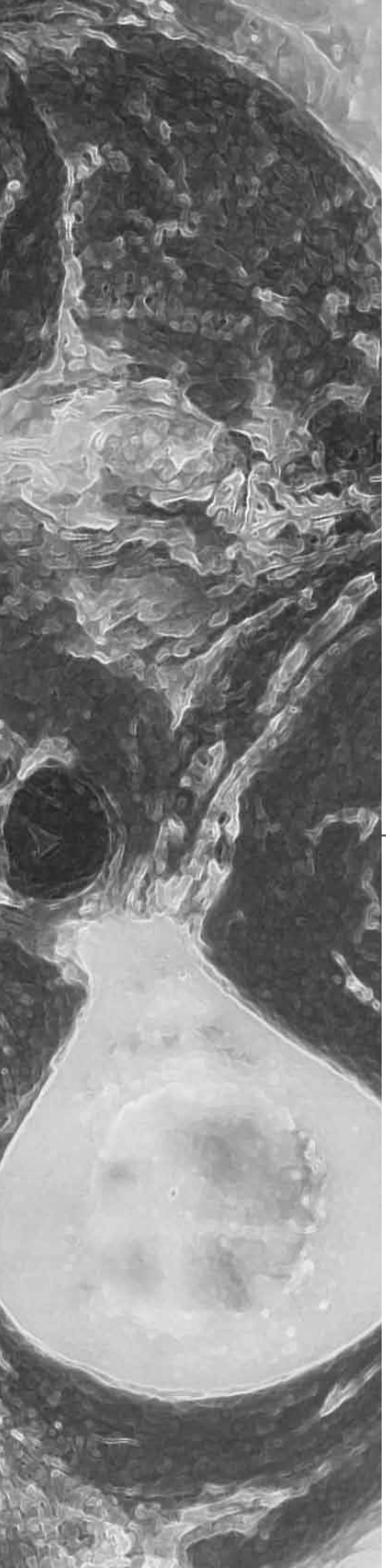

Chapter 5

Ultrasound Imaging, Cross-sectional Anatomy and Histology of the Sciatic Nerve: a Correlative Review

Nizar Moayeri, Geert-Jan van Geffen, Jörgen Bruhn, Gerbrand J. Groen

Submitted

Abstract

An optimal understanding of the ultrasound appearance of the sciatic nerve necessitates an active knowledge of equivalent cross-sectional anatomy. In this review, we provide an optimal matching between histology, anatomical cross-sections and ultrasound images of the sciatic nerve at its major block sites. The cross-sections were reconstructed in exactly the same planes as the ultrasound. Throughout its trajectory, the sciatic nerve contains numerous fascicles with connective and adipose tissue. The undulating course of the nerve fascicles within the sciatic nerve may explain its varying echogenic appearance during probe handling.

In a previous review, we described the relevant anatomic, histologic and ultrasound characteristics of the brachial plexus.[1] In the present survey, we present similar characteristics for the sciatic nerve. Sciatic nerve block is a very common lower extremity block in regional anesthesia. Although the sciatic nerve has the largest cross-sectional diameter in the human body, its ultrasonographical imaging is not always easy to interpret.[2] Fast and reliable identification requires a thorough knowledge of the topography and nature of nerves, and of adjacent structures.

From its formation in the lumbosacral region until its division in the popliteal region, the sciatic nerve descends in a curved way through various compartments bordered by bony and muscular structures. Unlike the brachial plexus, the sciatic nerve lies deeper to the surface without distinct accompanying vessels. Furthermore, its depth to the posterior skin varies from proximal to distal. Thus, variable viewing planes are required to optimize image quality. Continuous PART manoeuvres (Pressure, Alignment, Rotation, Tilting) of the probe are necessary to identify bony and soft tissue landmarks and the sciatic nerve.[3] Unfortunately, anatomical still-images in the same plane as the ultrasound images are generally only provided in standard transverse planes. Anatomical cross-sections in exactly the same planes as those observed during ultrasonography are lacking.

We employed data obtained by cryomicrotomy to reconstruct the optimal planes for an accurate comparison of ultrasonography and gross anatomy at the major locations of the sciatic nerve blocks. We used the same methods for acquiring data, reconstructions and histology, as applied in our earlier paper.[1] To reliably compare cryomicrotomy and ultrasound, the images have been matched in plane, location and angle. In this review, all presented anatomic images were acquired using a heavy-duty sledge cryomicrotome (PMV 450; LKB Instruments, Stockholm, Sweden). Consecutive transversal sections (interval, 76 μm) of a female upper leg specimen (82 yrs, body mass-index 23.3 kg/m2), frozen in carboxymethylcellulose gel at minus 30°C, were obtained. Histologic sections with an interval of 5 mm were stained using a modified Mallory-Cason procedure.[4] Although limitations have been described, cryomicrotomy is considered the gold standard to examine undisturbed topography of nerve structures.[5] However, post-mortem examination of the tissue yields an important drawback of the technique.

The aim of this study is to review those relevant anatomical aspects of the sciatic nerve in the upper leg that are necessary for a reliable pattern recognition in ultrasonography. The similarity in patterns of ultrasonography, gross anatomy and histology is highlighted. We believe that this will increase the insight in the structural appearance of the sciatic nerve, improve implementation of relevant local anatomy, and may help to understand why intraneural injections do not inevitably lead to neurologic damage.

Gross Anatomy

Sciatic nerve

The sciatic nerve is formed by the ventral rami of L4-S3, which converge at the level of the piriformis muscle. The sciatic nerve exits the pelvic region below the piriformis in 79.1% of cases. In 14.3% the nerve separates into two divisions proximal to the piriformis, one branch passing through the muscle, the other below it, whereas in 4.4% the branches pass above and below the muscle. In the remaining 2.2%, the entire nerve passes through

the piriformis undividedly.[6]

Infrapiriform region

Caudal to the piriformis muscle, the sciatic nerve curves, towards an almost direct course to the knee. From the upper part of lesser trochanter of the femur to the popliteal fossa, it runs in a more or less straight line, deep to the biceps femoris muscle.[7] In the infrapiriform region, the oblique running sciatic nerve lies deep, at about 7 cm distance to the posterior skin,[8] which makes optimal ultrasound imaging of the nerve difficult.

Deep to the gluteus maximus, the sciatic nerve then proceeds dorsal to the tendons of the triceps coxae (superior and inferior gemellus, internal obturator) and the quadratus femoris. This anatomical space has been described as subgluteal space.[8,9] In ultrasonography, it appears as a relative hypoechoic area with the honeycomb structure of the sciatic nerve at its deepest part.[8-11] Already in this area, the internal topographical pattern of the sciatic nerve fibers is formed. The nerve fibers of its major component, *i.e.,* tibial nerve, are located medially, those of the common peroneal nerve laterally in the sciatic nerve. More distally, the sciatic nerve is found exactly halfway between bony landmarks, greater trochanter and ischial tuberosity.[12]

Infragluteal region

The infragluteal region starts caudal to the lower edge of the gluteus maximus. The depression between the biceps femoris muscle and semitendinosus muscle would represent the cutaneous projection of the sciatic nerve,[13] and the starting point for ultrasound-guided infragluteal sciatic nerve block. Below the subgluteal fold, internal tendinous fibers of the long head of the biceps femoris serve as a soft tissue landmark for fast ultrasonographic identification of the sciatic nerve. Starting the ultrasound scanning from lateral, these internal tendinous fibers point directly to the sciatic nerve.[14]

From the infrapiriform toward the infragluteal region, the sciatic nerve lies between 4.5 and 8.5 cm deep to the posterior skin,[13] and at about 40% of the distance between posterior and anterior thigh.[15] At the subgluteal fold the average distance of the sciatic nerve to the posterior skin is 3.4 cm. More distally, it decreases to 2.7 cm to become again 3.4 cm at the midfemoral region.[16]

Midfemoral region

The midfemoral region is traditionally described as the middle of the line between the major trochanter of the femur and the popliteal crease. Due to the nearly vertical course of the sciatic nerve and its relative superficial position, this area is proposed as an alternative for ultrasound-guided sciatic nerve block.[17] During this trajectory, the sciatic nerve remains dorsal to the adductor magnus and ventral to the long head of biceps femoris.

Popliteal region

The popliteal part of the sciatic nerve begins where the sciatic nerve is not covered anymore by the biceps femoris. Compared to the midfemoral trajectory, two aspects have changed: the presence of adjacent large vessels (popliteal artery and vein) and the split of the sciatic nerve into two components, the tibial nerve (medially) and the common peroneal

nerve (laterally). The popliteal artery and vein lie 1 to 2 cm medial and deep to the sciatic nerve and form a recognizable landmark. In contrast to the inguinal region, in which the artery lays lateral to the vein, in the popliteal fossa the artery lays deep to and medial to the vein. The terminal part of the small saphenous vein near the sapheno-popliteal junction lies in close proximity to the tibial nerve, especially when the saphenous vein is dilated due to venous incompetence.[18]

Although the division of the sciatic nerve into two separate components has been described as early as the infrapiriform region, it generally occurs high in the popliteal fossa, on average 60,5 ± 27.0 mm (range, 0 - 115 mm) above the popliteal fossa crease.[19,20] The medial, tibial component of the sciatic nerve continues straight forward, deep in the popliteal fossa, parallel to the popliteal artery and vein. The lateral, common peroneal component continues after its separation laterally and more superficial, parallel to the distal tendon of the biceps femoris.

Microanatomy and echotexture

Basically, the micro-architecture of the sciatic nerve is similar to other peripheral nerves, *i.e.* an outer layer of epineurial connective tissue surrounding fat and connective tissue, and internal nerve fascicles surrounded by perineurium.[21] Although generally no distinct external division is visible until the popliteal region; internally, the sciatic nerve is already been divided into its tibial and common peroneal compartments in the infrapiriform region.[22] Both divisions are composed of fascicles and enveloped by epineurial connective tissue. The shape of the sciatic nerve is flat and large in the infrapiriform region and becomes more oval and smaller distally.[23] This is related to the size and amount of fascicles (neural tissue) and stroma and connective tissue (nonneural tissue) inside the epineurium. The sciatic nerve maintains its multifascicular pattern throughout its course.[21,24] This is in contrast to the microarchitecture of the brachial plexus, which changes from oligofascicular (interscalene) to multifascicular pattern (supraclavicular and further distal).[25-27]

The ultrasonographic appearance of the sciatic nerve is a reflection of its internal architecture and, thus, is similar to that of other peripheral nerves. Comparison between ultrasound scans of peripheral nerves and their corresponding histological slices demonstrate that the round hypoechoic areas seen with ultrasound coincide with neural tissue.[28-30] The hyperechoic background surrounding the hypoechoic areas correlates with the layers of connective tissue.[23] In general, the sciatic nerve presents as a tubular hyperechoic structure with parallel linear hypoechoic lines in long axis visualisation and as a speckled (honeycomb) structure in short axis visualisation.[12,31] Varying the insonating angle of the transducer reduces its echogenic appearance, but to a smaller degree than in muscles and tendons.[31]

For imaging the sciatic nerve, linear probes with a frequency of 7-13 MHz may be used at the upper thigh, lower inner thigh and popliteal fossa.[32] Curvilinear transducers with frequencies of 2-5 or 4-7 Mhz can provide significant advantages in the visualisation of the sciatic nerve at the midfemoral, infragluteal and gluteal region.[9,12,33] The curved probe allows scanning of a wider and deeper anatomic region than a linear probe. Although it facilitates the visualisation of bony and soft tissue landmarks, it is at the expense of tissue resolution.

An ultrasound overview of the sciatic nerve at various anatomical locations has been provided in both anesthesiological and radiological literature.[2,34] The alignment of the probe for various locations along the course of the sciatic nerve could be summarized as follows:

a transversal oblique plane for the gluteal and infragluteal location, and a transversal plane for the section between the infragluteal and popliteal region (Figure 1). Continuous PART (Pressure, Alignment, Rotating and Tilting) manoeuvres with the probe are necessary to maximize reflection at nerve/tissue interfaces for an optimal image quality.[3]

Infrapiriform area

The sciatic nerve emerges inferior to the piriformis muscle and enters the infrapiriform region (Figure 2A,B). Here, the sciatic nerve lies at its maximum depth, making it difficult to visualize by ultrasound. Oblique to transversal alignment of the probe with cranial to caudal movements localizes the ischium as a hyperechoic line with refracted shadowing. Slight tilting reveals the hyperechoic tendon of the internal obturator (Figure 2 C,D). The sciatic nerve is predominantly visualized as a hyperechoic, flat and thin elliptical structure.[12] In 87% of cases, good quality images could be obtained.[12] Superficial to sciatic nerve, a more hypoechoic gluteus maximus is seen (Figure 2 C,D). At this location, the sciatic nerve is poorly delineated and the internal architecture shows little detail (Figure 2 E,F).

Eisenberg *et al.* visualized the wide sciatic nerve in long axis and used an in-plane needle approach to block the sciatic nerve. Advantages of this technique are the good visualization of the piriformis, gluteus maximus and gemelli muscles, the ileum and the gluteal inferior artery medial to the nerve.[35]

Infragluteal area

Between the ischial tuberosity medially and the greater trochanter of the femur laterally, the sciatic nerve descends into the infragluteal area (Figure 3 A,B). The bony structures generate dense hyperechoic lines, which can be used as landmarks. The sciatic nerve appears as a hyperechoic, flat- to oval-shaped structure with an internal "speckled" architecture (Figure 3 C-F).[12] Again, the actual amount of the fascicles is higher than seen by ultrasound.[36] Recently, an alternative and fast approach was reported between the subgluteal fold and the midfemoral area.[14]

In obese patients, the sciatic nerve can be blocked via the anterior approach. The sciatic nerve is visualised after internal rotation of the leg at 45 degrees. The sciatic nerve is seen as a round hyperechoic, highly anisotropic formation deep to the quadriceps muscle, attached to the acoustic shadow of the femur.[37] Because of the deep location and the high anisotropic nature of the nerve, this might not be the preferred approach to the sciatic nerve for inexperienced anesthesiologists. However, recently an anterior approach to the sciatic nerve in a slightly exorotated leg was found as easily and successfully as the posterior approach using ultrasound guidance.[10]

Midfemoral area

In this region, the sciatic nerve is typically surrounded by muscles (biceps femoris, adductor muscles) and fascial planes (lateral intermuscular septum) (Figure 4 A,B). Identification of the sciatic nerve has been described as good to excellent.[16,17,38] The sciatic nerve appears as speckled hyperechoic with a fascicular structure, surrounded by a well-defined hyperechoic connective layer (Figure 4 C-F).[17,39]

Popliteal Area

The distal sciatic nerve has a round to oval, hyperechoic shape. In its most superficial location, the sciatic nerve divides into tibial and common peroneal (fibular) nerves before the popliteal crease (Figure 5 A,B). The internal aspect of the nerves shows as speckled hypoechoic areas (fascicles) mixed with hyperechoic adipose and connective tissue, surrounded by hyperechoic fascia (Figure 5 C,D),[36] similar to its histological view (Figure 5 E,F).

At the level of the sciatic nerve bifurcation, difficulties in ultrasonic visibility have been described.[19,40,41] These are attributed to differences between the two nerves in angulation, spatial orientation, depth and internal architecture, which complicate simultaneous imaging of both nerves exactly perpendicular to their axis. Moreover, the nerves are embedded in fat which gives less tissue contrast than muscles. The distal sciatic nerve, before its bifurcation, can be highlighted by passive or active dorsiflexion and plantar flexion of the foot.[42] During dorsiflexion, the tibial component moves towards the posterior skin of the leg, and during plantar flexion the peroneal component moves towards the posterior skin of the leg. This phenomenon occurs because the tibial nerve lies posterior to the axis of the talocrural joint and is pulled during dorsiflexion. The peroneal nerve lies anterior to the axis of the talocrural joint and is pulled during plantar flexion.[43]

Using ultrasound, the exact bifurcation site of the sciatic nerve can be traced, even up to the infragluteal region. Tsui *et al.* proposed a "traceback" approach using the popliteal blood vessels as guidance for ultrasonographic identification of the sciatic nerve.[44] First, the popliteal artery and vein are identified. Then, the tibial nerve is visualised as a round hyperechoic structure lying near the midline, superficial and lateral to the popliteal artery and vein. The bifurcation and distal sciatic nerve can be identified by moving the probe cephalad along the tibial nerve. The common peroneal nerve is less clear, but also appears as a speckled hyperechoic structure, superolateral to the tibial nerve. More proximal, the distinct common peroneal and tibial nerves converge to one single large oval hyperechoic sciatic nerve.

Discussion

The ultrasound image of the sciatic nerve is dependent on its shape, internal architecture, spatial orientation and adjacent structures. Originally, the echotexture of the sciatic nerve was determined by low frequency ultrasound (2-5 MHz), necessary because of the deep location of the sciatic nerve in the investigated areas.[12,23,29,32] However, this technique offers limited resolution and shows only a rough detail of the internal topography of the nerve, whereas small diameter fascicles are missed.[36]

Silvestri *et al.* reported that the total amount of fascicles observed by ultrasound is much lower compared to the actual number observed by light microscopy.[36] They observed with 15 MHz ultrasound, only one-third of the number of fascicles in the sciatic nerve. This suggests that even with the use of high-frequency ultrasound only a fraction of the actual amount of the fascicles is seen. Although ultrasound devices with higher frequency (up to 20 MHz) are available, their usefulness for a more accurate and detailed image is limited due to the depth of the sciatic nerve.

Whereas ultrasonographic visualisation of detailed internal architecture of nerves may

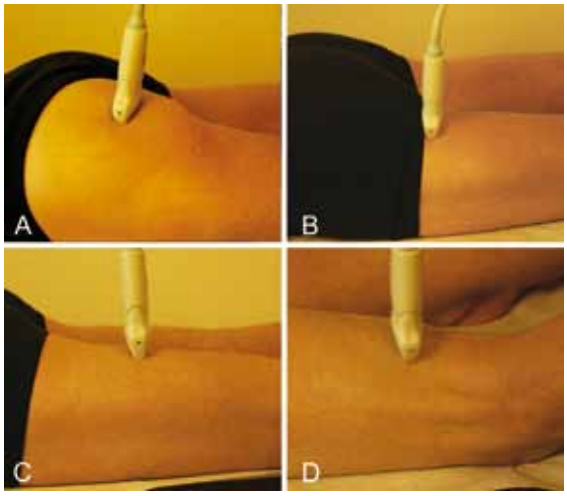

Figure 1. Survey of probe positions in the midgluteal/infrapiriformis (A), infragluteal (B), midfemoral (C), and popliteal (D) area.

be more important for non-invasive diagnosis of neuropathies,[45] its value for regional anesthesia may seem limited, especially during the performance of ultrasound-guided nerve blocks. However, this is not the case when explanations need to be found for the apparent lack of long-term neurologic damage after intraneural injection.[46] Application of low current intensity stimulation (between 0.2 and 0.5 mA) does not prevent intraneural needle placement during popliteal sciatic nerve block,[47] while the same stimulation parameters do not discern between extraneural and intraneural needle tip placement.[48] Even the use of ultrasound-guided needle placement cannot prevent intraneural injection.[49,50]

In this respect, the recent findings of Sala-Blanch *et al.* are of interest.[51] They found that insertion of a sharp-beveled needle through the entire cross-section of a post-mortem sciatic nerve resulted in damage of 1 intraneural vessel and 3.2% of the number of fascicles. With blunt-beveled needles no damaged fascicles were observed. Thus, it seems that the consistency and amount of extrafascicular tissue is important.

The non-neural tissue consists of connective and adipose tissue with per cross-section on average 14 blood vessels with a mean diameter of about 0,2 mm and an artery-to-vein ratio of 3:1.[51,52] Recently, we found a significant change in the neural-to-nonneural ratio between the proximal and distal sciatic nerve. In the midgluteal and subgluteal areas this ratio was 2:1 compared to 1:1 in the midfemoral and popliteal areas.[24] These observations on the consistency and amount of extrafascicular tissue would explain the higher vulnerability for neurologic sequelae in the proximal sciatic nerve blocks.[53]

Conclusion

Reliable and fast interpretation of ultrasonographical images necessitates thorough knowledge of cross-sectional anatomy. In this review, by detailed (sono)anatomical descriptions, the major block sites of the sciatic nerve, *i.e.,* infrapiriform, infragluteal, midfemoral and popliteal, are highlighted. The shown correlations between ultrasound images, cross-sectional anatomy and histology should facilitate a reliable and fast identification of anatomical relationships and recognition of sciatic nerve. The shown internal architecture of the sciatic nerve may help to better understand the relatively low risk of neurologic damage after inadvertent intraneural injection.

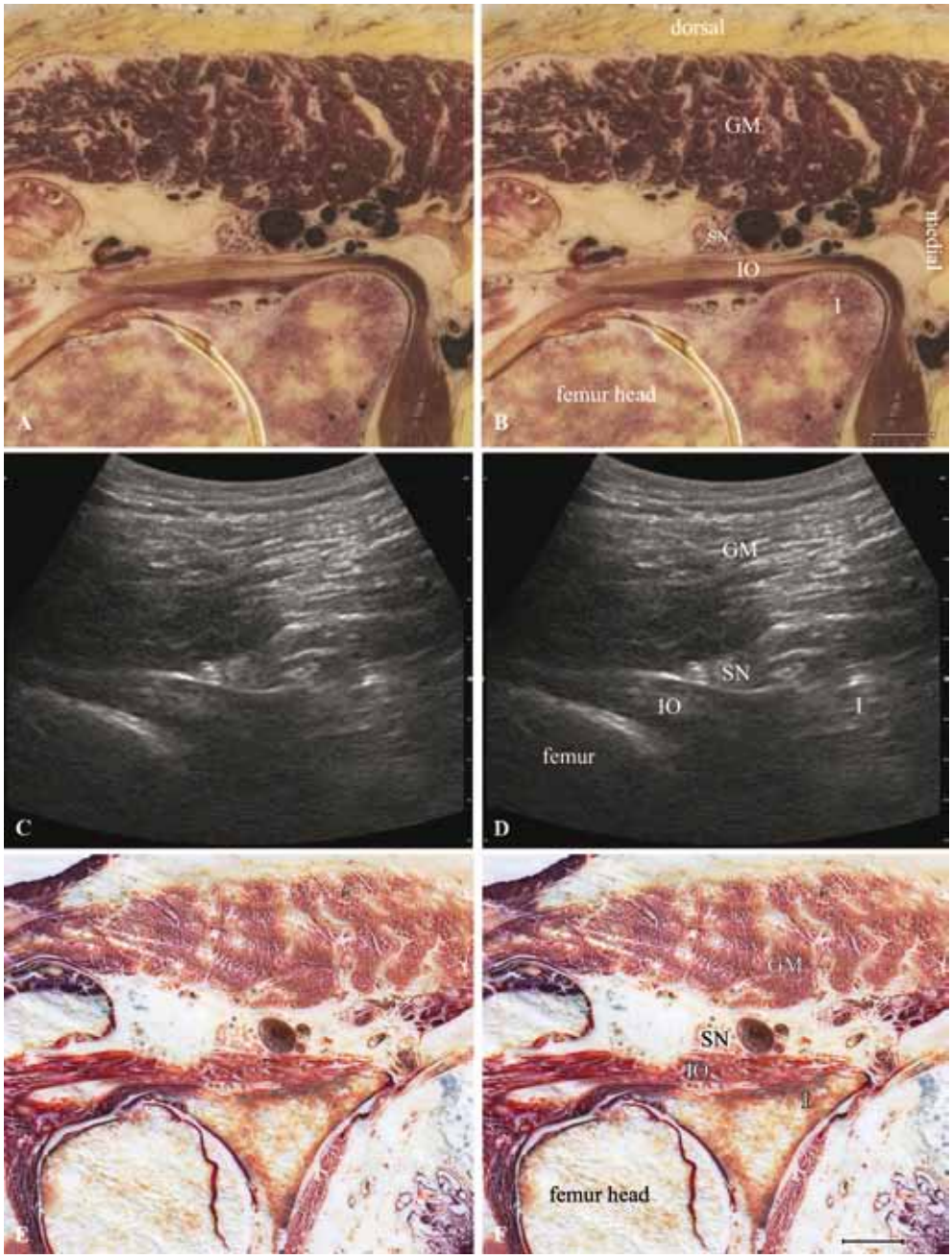

Figure 2. Infrapiriform region. Transversal oblique views of the sciatic nerve and adjacent structures, left column without labels, right column with labels. (A, B) Reconstructed anatomical views from digitized cryomicrotomy cross-sections; (C, D) ultrasonographic short axis views showing the sciatic nerve as hyperechoic structure; (E, F) histological section (Mallory-Cason trichrome staining) comparable to midgluteal transversal axial oblique view. GM, gluteal maximus; SN, sciatic nerve; IO, internal obturator; I, ischium. Bar = 1 cm.

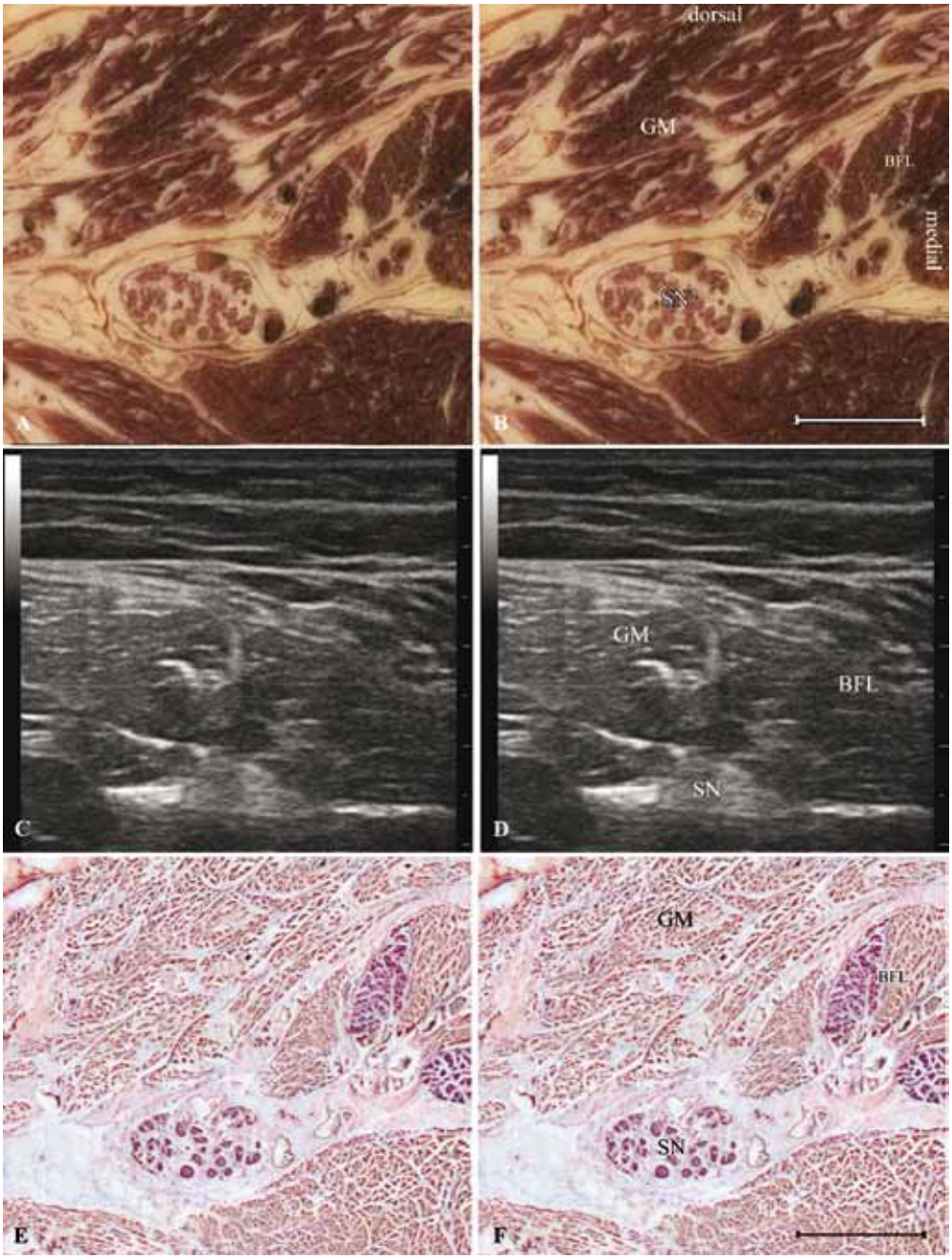

Figure 3. Infragluteal region. Transversal oblique views of the sciatic nerve and adjacent structures, left column without labels, right column with labels. (A, B) Reconstructed anatomical views from digitized cryomicrotomy cross-sections; (C, D) ultrasonographic short axis views showing the multiple fascicles structure of the infragluteal sciatic nerve; (E, F) histological section (Mallory-Cason trichrome staining) comparable to infragluteal sciatic nerve transversal oblique view, demonstrating the multifascicular nature of the sciatic nerve. GM, gluteau maximus; SN, sciatic nerve; BFL, biceps femoris long head. Bar = 1 cm.

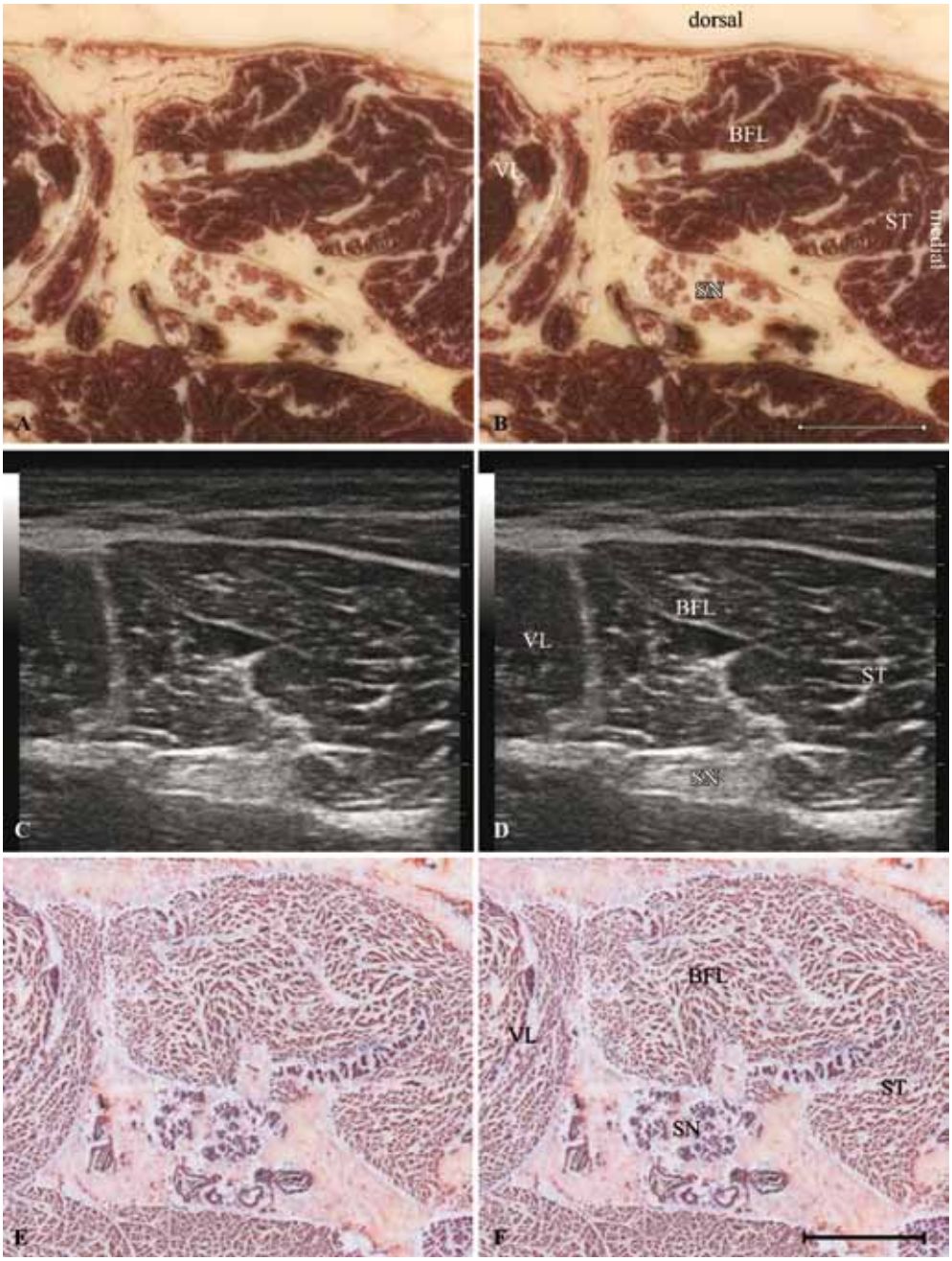

Figure 4. Midfemoral region. Transversal views of the sciatic nerve and adjacent structures, left column without labels, right column with labels. (A, B) Reconstructed anatomical views from digitized cryomicrotomy cross-sections; (C, D) ultrasonographic short axis views; (E, F) histological section (Mallory-Cason trichrome staining) comparable to midfemoral, transversal view. SN, sciatic nerve; BFL, biceps femoris long head; ST, semitendinosus. Bar = 1 cm.

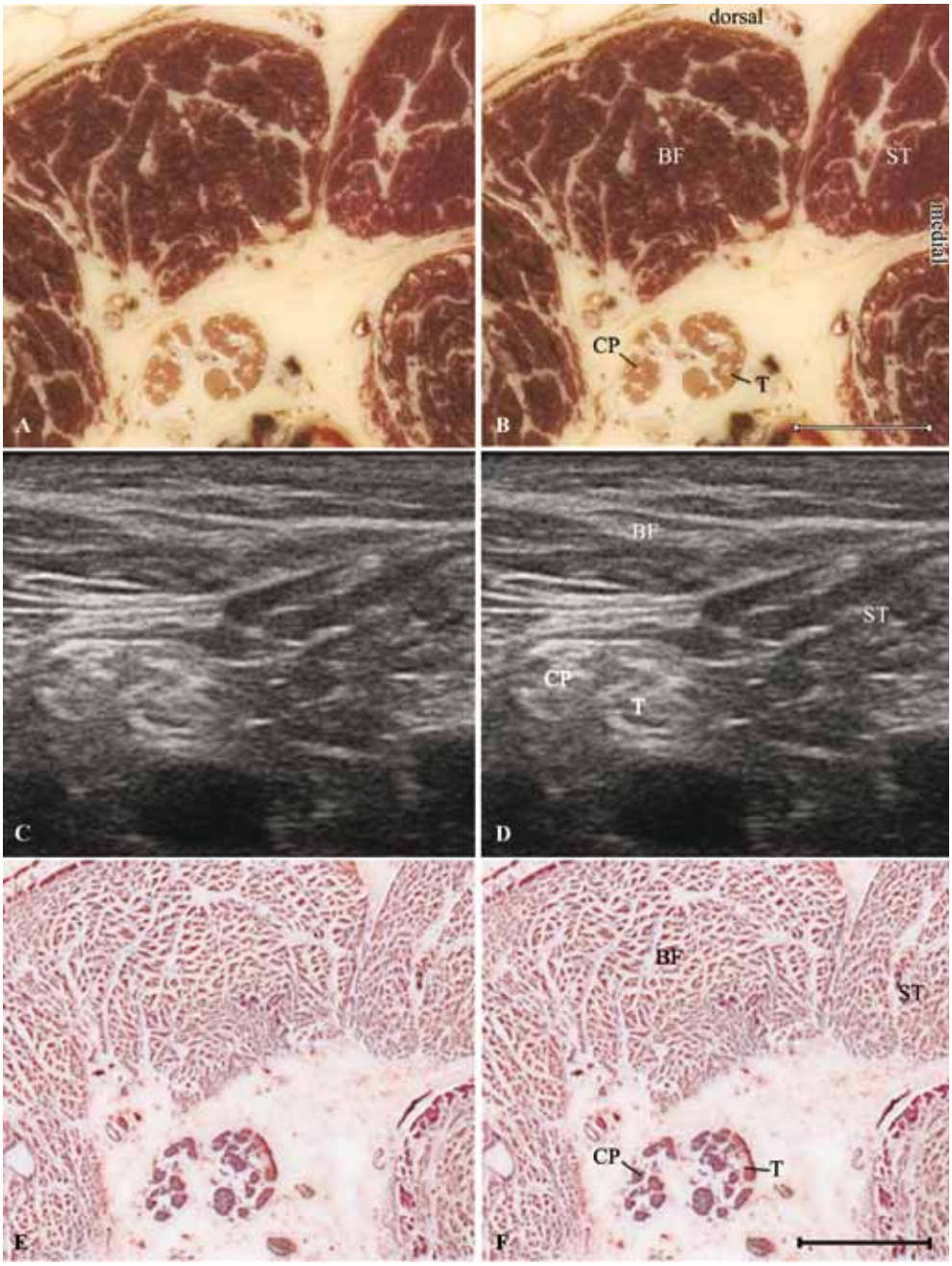

Figure 5. Popliteal region. Transverse views of the sciatic nerve and adjacent structures just before the actual bifurcation of the sciatic nerve, left column without labels, right column with labels. (A,B) Reconstructed anatomical views from digitized cryomicrotomy cross-sections; (C,D) ultrasonographic short axis views; (E,F) histological section (Mallory-Cason trichrome staining) comparable to popliteal transverse view. CP, common peroneal nerve; T, tibial nerve; BF, biceps femoris; ST, semitendinosus. Bar = 1 cm.

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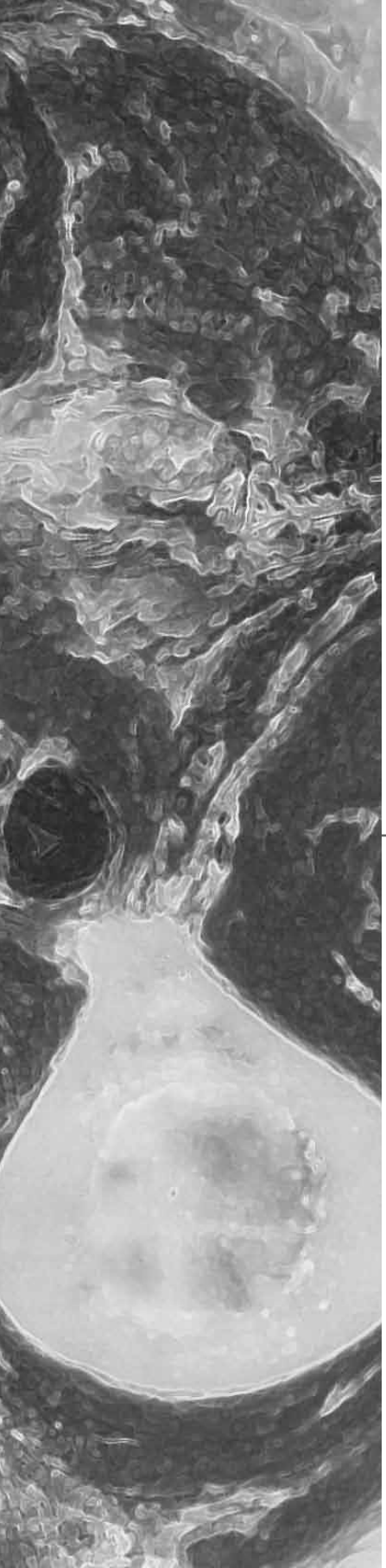

Chapter 6

Intraneural Injection of Local Anesthetics and Nerve Injury. A Systematic Review

Nizar Moayeri, Walid Moudrous, Martina S. Frijlink, Alain Borgeat, Gerbrand J. Groen

Submitted

Abstract

Background **Among etiologic factors for the development of neurologic deficit after peripheral nerve block, intraneural injection of local anesthetics has been proposed as a risk factor. In this systematic review, we assessed the overall risk by collecting all available evidence of the relation between intraneural injection of local anesthetic and risk of nerve damage.**

Methods **All relevant databases were systematically searched for studies published until July 31, 2009 where the primary intent was to investigate the effects of intraneural injection of local anesthetics on nerves. Studies were assessed for final analysis based on inclusion and exclusion criteria.**

Results **Four human and 6 animal studies remained for final analysis. In all human studies, ultrasound was used to confirm intraneural injection. The risk of transient (< 3 weeks) neurologic deficit was < 4%. In animal studies, a total number of 368 intraneural injections were conducted of which 233 intrafascicular and 12 with high injection pressure. The percentage of neurologic dysfunction after intrafascicular injection was 62.7 with a risk ratio of 62.9 (95%CI; 13.1−303.2), compared to no evidence of nerve damage after interfascicular injection. All injections with high pressure (≥ 20 PSI) were associated with neurologic deficit (risk ratio 32.4 [95%CI; 4.8−218.6]).**

Conclusion **There seems to be a slightly increased risk of transient neurologic dysfunction after ultrasound-guided intraneural injection. However, intrafascicular injection (high injection pressure) is associated with a high risk of nerve damage. On the contrary interfascicular injection (low injection pressure) does not seem to lead to elevated risk.**

The risk of neurologic damage after peripheral nerve block is relatively low. The risk of post block neuropathy is estimated to be less than 3% for the upper extremity blocks and less than 0.3% for the lower extremity blocks.[1] In the majority of cases, the nerve damage is transient, but may last for weeks or sometimes several months. Permanent nerve damage is very rarely observed.

Several etiologic factors of neurologic complications have been considered. Neurotoxicity, type and concentration of the local anesthetic,[2] injection pressure,[3] and patients' characteristics[4-6] are identified as possible cause of nerve damage. An underestimated factor is the type of surgery. The occurrence of transient neurologic dysfunction of the brachial plexus, for example can be as high as 30% after shoulder arthroscopy.[7]

In addition to the aforementioned factors, intraneural injection of local anesthetics is believed to be an important source of nerve damage.[8] In the past, several animal studies have addressed this issue, sometimes with contradictory findings. Several case reports have suggested the possible association between intraneural injection and nerve injury.[9,10]

The clinical application of ultrasound as a visual guidance of the needle to the nervous structures has recently led to several reports dealing with the relation between intraneural injection and nerve damage,[11-14] with partially contradictory results compared to animal studies. To date, a systematic overview of data concerning intraneural injection and nerve damage is lacking. The objective of this systematic review is to gather and confirm or not evidence on the relation between intraneural injection of local anesthetics and the development of neurologic damage and subsequently to assess relative risk if any.

Materials & Methods

A systematic search was conducted in MEDLINE, Embase, Cochrane Library, ISI Web of Knowledge, and Scopus for papers published between 1950 and July 31, 2009. The following keywords and their synonyms were used in input fields of title/abstract, Mesh and Emtree words: "intraneural," "transneural," "intraepineural," "transepineural," "intraperineural," "transperineural," and "nerve," "nervous," "neural," "neurologic," and "injury," "damage," "complication," "dysfunction," "deficit," "neuropathy". Further, reference sections of all relevant publications were examined to capture any additional studies. The detailed workout of inclusion and exclusion criteria is listed in Figure 1. Only studies in which the stated objective was to investigate intraneural injection and nerve damage were considered for the present review. The following criteria were considered for inclusion in the study: original studies describing injection of any local anesthetic intraneurally (either inside epineurium or perineurium), confirmed either by exposing the nerves and visually inserting the needle inside the nerve, or with ultrasound guidance (US). In addition, the presence or absence of any nerve damage was assessed either by measurement of the sensory or motor function or the intensity of pain after 48 hours, or microscopical evidence of any signs of nerve degeneration during the follow-up period.

The quality of evidence for each study was graded (highest to lowest: I – III; table 1) according to the criteria described by Harris *et al.*[15] Only adverse neurologic sequelae that were observed as related to or associated with intraneural injection are addressed in this review. Injection of solutions other than local anesthetics, studies investigating complications such as abscess or infection, neuraxial studies, permanent blocks, perineural catheters, and case reports were excluded from final analysis.

Definition

The classical observations by Key and Retzius laid the foundations for the current terminology.[16] They proposed a subdivision into epineurium, perineurium, and endoneurium (Figure 2). The epineurium is the outer layer which consists of a condensation of connective tissue that surrounds the fascicles of uni- and multifascicular nerves. The cross-sectional surface area of the epineurium contains 30 to 75% of connective tissue, depending on the region of the body and its proximity to the origin or roots.[17,18] The perineurium is the actual ensheathment of the bundles of nerve fibers. It is composed of flattened polygonal cells, the number of which depends upon the diameter of the fascicle. The most inner connective layer, the endoneurium, encloses the individual nerve fibers and comprises the intrafascicular connective tissue. To maintain a uniform nomenclature throughout this review, either the term "intrafascicular" (between the peri- and endoneurium) or interfascicular (between the epi- and perineurium) is used. In some of the included studies, *intrafascicular* and *interfascicular* injection were referred to as "intraneural" and "perineural", respectively. A subgroup analysis was conducted between human and animal studies. In the animal studies, the

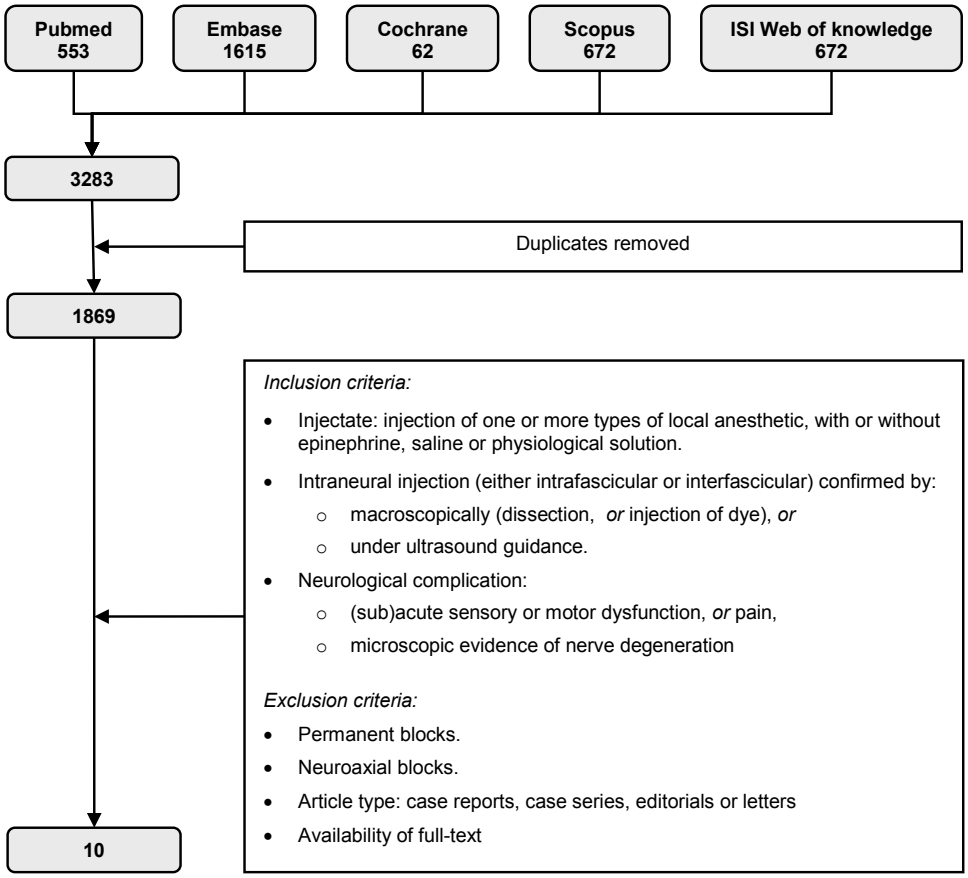

Figure 1. Flowchart of the search method.

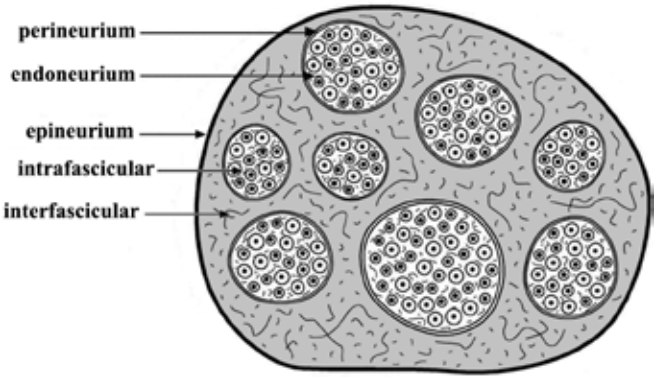

Figure 2. Cross-sectional overview of peripheral nerve.

analysis was based either on intrafascicular or interfascicular injection. An overall incidence rate of neurologic complications after application of intraneural injection was based on the number of events relative to the total number of injections.

Statistical analysis

When possible and applicable, risk ratios (RR) and confidence intervals (CI) were calculated for the pooled studies and for dichotomous results (nerve damage, intrafascicular injection, injection pressure). Due to the sparsity of data, either in terms of low event rates or small study size, the analysis method according to Mantel-Haenszel was used for calculation of RR and CI. The Cochran Q test was applied to determine the heterogeneity between the source studies. Significance was considered at $P < 0.05$. All statistical analyses were performed using Review Manager Version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2008, Copenhagen, Denmark).

Results

Our search yielded 1869 results, of which 10 studies met our final inclusion criteria. Table 2 lists the baseline characteristics of the included studies. To compare objectively the findings of the included studies, all human and animal studies were assessed separately. When applicable and only for the animal studies, a sub-analysis was conducted between intrafascicular and interfascicular injections.

Table 1. Quality of evidence

Grade I	Evidence obtained from at least one properly randomized controlled trial.
Grade II-1	Evidence obtained from well-designed controlled trials without randomization.
Grade II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
Grade II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
Grade III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 2. Characteristics of published studies of the association between intraneural injection and neurological dysfunction included in the systematic review

	Methods					Findings
Studies (species; nerve)	*Local anesthetic*	*Injections (n)*	*Location*	*Controls?*	*Follow-up*	*Complications*
Selander *et al.* 1979 *(rabbit; SN)*	Bupicavaine: 0.05-0.5ml (5 - 40mg/ml)	64	Intrafascicular	Saline	10-14 days	Bupivacaine: +: 41; ++: 18; +++: 5 Saline: 11:+, 4:++, 1:+++
Gentili *et al.* 1980 *(rat; SN)*	0.05-0.1ml: lidocaine 1-2%†; bupivacaine 0.5%†; mepivacaine, tetracaine (1%); procaine 2%	260	Intrafascicular interfascicular	Saline	1 and 2 hrs 9, 12 days	Intrafascicular: -: 12; +: 24; ++: 59; +++: 47 Extrafascicular: none.
Westerlund *et al.* 1998 *(rat; SN)*	0.01-0.02 ml of lidocaine 2%	64	Intrafascicular interfascicular	Saline	1, 2, 4, 8 weeks	MFS = 0; no muscle atrophy, no trophic skin changes, no microscopic changes.
Hadzic *et al.* 2004 *(canine; SN)*	4 ml of lidocaine† 2%	14	Intrafascicular interfascicular	None	first 6 hrs, 1 week	Interfascicular and Intrafascicular (≤11 PSI): return motor function within 3 hours. Intrafascicular (≥25 PSI): persistent motor deficit; microscopy: significant nerve damage.
Iohom *et al.* 2005 *(rat; SN)*	0.2 ml of ropicavaine 0.2-0.75%	39	Intraneural	Saline	1, 4, 7, 11, 15, 18, 21, 67 days	SFI = normal; no microscopic nerve degenerations.
Kapur *et al.* 2006 *(canine; SN)*	4 ml of lidocaine 20 mg/ml	15	Intrafascicular interfascicular	None	intervals of 2 hrs until 24 hrs, 2, 3, 4, 5, 6, 7 days.	Interfascicular and Intrafascicular (≤12 PSI): return motor function within 3 and 12 hours, resp. no nerve damage. Intrafascicular (≥20 PSI): moderate paresis after 1 week, significant nerve damage.
Bigeleisen *et al.* 2006 *(human; BP)*	2-3 ml of bupicavaine 2.5 mg/ml and lidocaine 10 mg/ml	26	Intraneural	None	96 hrs, 3 weeks, 6 months	96 hrs: localized pain in 3 patients; 3 weeks and 6 months: no complications.
Bigeleisen *et al.* 2009 *(human; BP)*	5 ml of bupicavaine 2.5 mg/ml and lidocaine 10 mg/ml	39	Intraneural	None	72 hrs, 3 weeks, 6 months	72 hrs: localized pain in 3 patients; 3 weeks: 2 patients with numbness**; 6 months: no complications.
Sala-Blanch *et al.* 2009 *(human; SN)*	40 ml mepivaciane 1.2%	28	Intraneural	None	72 hrs, 3 wks, 6 months	No neurologic dysfunction reported
Robarts *et al.* 2009 *(human; SN)*	30-40 ml of 0.5% ropi- or 1.5% mepivacaine	20	Intraneural	None	24 and 48 hrs	No neurologic dysfunction reported

* concentration µm/ml; ** neurological signs likely caused by surgery. SN: sciatic nerve; BP: brachial plexus; †: with epinephrine.
Selander *et al.*: +: none or insignificant axonal degeneration; ++: significant but < 50% of axonal degeneration; +++: ≥50% of axonal degeneration.
Gentili *et al.*: -: no evidence of nerve damage; +: minimal nerve injury with occasional nerve fiber injury; ++: moderate nerve injury with focal axonal and myelin damage; +++: severe nerve fiber injury with widespread axonal and myelin degeneration.
SFI: sciatic function index, normal between 0 and 10; -100: complete loss of nerve function. MFS: motor function scale, range between 0 (normal) and 3 (paralyzed).

Human studies

The search identified 4 recent human studies.[11-14] The quality evidence score of all human studies was graded II-2 (Table 1). Sala-Blanch *et al.* investigated the incidence of intraneural injection in nerve stimulator-guided popliteal sciatic nerve block.[14] In this study, ultrasound was applied to visualize the sciatic nerve before and after injection. Intraneural injection was defined as an increase in nerve area by more than 15% and at least one additional ultrasound criterion. After injection of 40 ml of local anesthetic, the authors found evidence of intraneural injection in 66% of cases (28 out of 42 patients). After a follow-up period of 1 week, no sensory or motor dysfunction was observed in any of the intraneurally injected patients. Additional relevant observations were faster onset time of the block in the intraneurally injected cohort of patients and normal injection pressure (< 20 PSI) in all injections.

Recently, in a similar study, intraneural injection at low stimulation current (0.2-0.4 mA) was conducted on the popliteal sciatic nerve in 20 patients.[11] Intraneural presence after injection of 30-40 ml of local anesthetic was confirmed by increase in nerve diameter and compartmentalization of the nerve within the epineurium. No patients reported neurological dysfunction after a follow-up period of 24 and 48 hours.

Bigeleisen *et al.* conducted two studies on the brachial plexus.[12,13] In the first study, ultrasound-guided intraneural injection of the axillary brachial plexus was conducted using a maximum of 3 ml of local anesthetic.[12] In all targeted nerves, at least one characteristic sign such as appearance of a halo ring or swelling of the nerve diameter was seen. Of the 26 intraneurally injected patients, 3 reported tenderness at the injection site, which resolved at 3 weeks. No sensory or motor dysfunction were reported after a follow-up period of 6 months.

In a more recent study a maximum of 5 ml of local anesthetic was injected intraneurally to confirm intraneural presence of the needle tip verified by ultrasound.[13] Puncture and indentation of the nerve wall followed by expansion of the nerve area were seen in 39 of the intraneurally injected patients. In this cohort, 3 patients reported pain at the injection site, which resolved at 3 days, and 2 patients reported numbness at the surgical area, which resolved at 5 weeks. After completion of the follow-up period of 6 months, no sensory or motor deficit was seen in any patient.

Although the studies on the human subjects are not comparable with regard to the applied methodology (*e.g.* difference in the type and amount of local anesthetic, or type of needle) the combined results of the risk of neurologic sequelae shows that the short term incidence (less than 3 weeks) of neurologic dysfunction after intraneural injection of local anesthetics is approximately 3.9% (n = 5/127). However, the risk of persistent nerve dysfunction after a relatively long term period (6 weeks to 6 months) is negligible. No distinction could be made between application of the local anesthetic either intrafascicularly or interfascicularly as ultrasound does not allow such distinction.

Animal studies

The search identified 6 animal studies.[3,19-23] The quality evidence score of the animal studies ranged between I and II-1 (Table 1). In their fundamental study, Selander *et al.* investigated the effect of intrafascicular injection of local anesthetics on adult albino

rabbits.[21] The sciatic nerves were exposed using a sterile, atraumatic technique. In 32 rabbits, intrafascicular injections were made with various concentrations of bupivacaine 0.05 ml or 0.5 ml (with or without adrenaline). For controls, saline in the same amount as bupivacaine was injected intrafascicularly. In addition, 24 rabbits received the same amount of bupivacaine or saline around the exposed sciatic nerve. It is unclear how intrafascicular injections were guided or assessed. After a follow-up period of 10 to 14 days, significant microscopical evidence of axonal degeneration was observed in 60% of cases injected with 0.05 ml of bupivacaine (5 mg/ml); 75% of cases injected with 0.05 ml of bupivacaine (10 mg/ml); 12.5% of cases injected with 0.5 ml of bupivacaine (20 mg/ml); and 50% of cases injected with 0.5 ml of bupivacaine (40 mg/ml). In contrast, intrafascicularly injection of 0.05 ml of saline caused nerve damage in 28% of cases. Compared with injection around the sciatic nerve, physiologic saline or bupivacaine (5 and 10 mg/ml) did not induce significant degeneration. However, in 12.5% and in 50% of cases, significant degeneration was observed with bupivacaine 20 and 40 ml, respectively.

In another classical study, Gentili *et al.* investigated the possible toxic effects of intra- and interfascicular injection of various local anesthetics in the sciatic nerves of Wistar rats.[19] A total of 142 intrafascicular injections were conducted with various concentrations of lidocaine, bupivacaine, mepivacaine, tetracaine and procaine, after surgical exposure of the sciatic nerve. Similar amounts of saline were used as control. It is unclear how intrafascicular injections were assessed. Using both light and electron microscope, the nerves were examined after 1 to 2 hours and 9 to 12 days after injection. In the cohort of interfascicular injections, no evidence of nerve damage was reported in both local anesthetic and saline (control) group. Also, intrafascicular injection of saline showed no significant damage to the nerve in early (1-2 hrs) or late (10-12 days) follow-up. In the cohort of intrafascicular injections with local anesthetics, however, severe nerve fiber damage was seen after injection of 0.1 ml of 2% procaine, 1% tetracaine, or 2% lidocaine. Immediate abnormalities of the myelin sheaths, as well as widespread damage throughout the fascicles with degeneration of the axons and myelin, were seen after 10-12 days. Moderate nerve injury was associated with injection of 0.1 ml 1 or 2% lidocaine or 0.5% mepivacaine, both with epinephrine. No evidence of active axonal damage was observed after intrafascicular injection of 0.5 % bupivacaine or 1% mepivacaine, both without adrenaline.

To compare the effects of intrafascicular (intraneural) and interfascicular (perineural) injection of various agents (including lidocaine), Westerlund *et al.* used an experimental rat sciatic nerve model.[23] After surgical exposure of the sciatic nerve on both sides, 16 male Spraque-Dawley rats were injected with 0.01-0.02 ml of 2% lidocaine either intrafascicularly or interfascicularly. A control group of 16 animals received the same amount of saline. Again, no description was given on how the intrafascicular injection was assessed. During a follow-up period of 1, 2, 4 and 8 weeks, motor examination score (muscle function score, gastrocnemius muscle atrophy, trophic skin changes) as well as light microscopical evaluation were used to assess possible nerve damage. The lidocaine- and saline-injected rats did not show noticeable abnormalities in their muscle function, nor skin changes, for either intrafascicular or interfascicular injections. In addition, on light microscopical examination, all saline-injected nerves appeared intact. Neither lidocaine nor saline caused detectable morphological changes after interfascicular injections. However, the intraneurally-injected animals with lidocaine showed focal nerve damage associated with patch nerve fiber loss and an increased number of endoneural cells. Generally, axonal spouting was observed after

1-2 weeks after damage caused by lidocaine, which became myelinated after 4 weeks.

More recently, Hadzic *et al.*[3] investigated the effects of intrafascicular and interfascicular injection of 4 ml of 2% lidocaine with adrenaline on canine's sciatic nerve. After surgical exposure of the sciatic nerve, the injection needle was placed under direct light microscopic guidance either intrafascicularly or interfascicularly followed by a total of 14 injections. Continuous measurement of pressure during injection was provided with an in-line manometer. Blind motor examination as well as light microscopical examination were conducted at 1 hour intervals for up to 6 hours and subsequently daily for up to 1 week. All interfascicular injections (n=7) were associated with low injection pressure (≤ 11 PSI) and did not cause any motor deficit or damage to the sciatic nerve architecture on microscopical examination. In addition, intrafascicular injection with low injection pressure (n=3) had no deleterious effect on the sciatic nerve. However, intrafascicular injections with high injection pressure (≥ 25 PSI; n=4) caused persistent motor deficit after 1 week. On their microscopical examination, varying degrees of damage to the neural architecture were observed ranging from mechanical disruption and delamination to fragmentation of the myelin sheath and marked cellular infiltration.

In a similar study, Kapur *et al.*[21] used 15 canines to inject 4 ml of lidocaine 20 mg/ml either intrafascicularly (n=20) or interfascicularly (n=10) with continuous monitoring of pressure and directly under microscopical guidance. Motor examination was assessed at 1 hour interval for up to 8 hours and subsequently daily for up to one week, followed by light microscopical examination. All interfascicular-injected sciatic nerves (injection pressure ≤ 5 PSI) recovered normal motor function within 3 hours. Their microscopical examination revealed normal architecture of the nerve. In addition, intrafascicular-injected sciatic nerves with low pressure (≤ 12 PSI; n=12) regained normal motor function within 24 hours. Moreover, their microscopical examination showed no damage to the neural architecture. The intrafascicular-injected sciatic nerves with high injection pressure (≥ 20 PSI; n=8), however, had persistent paresis and reflex abnormality after the follow-up period (7 days). In addition, their pathohistological examination showed marked nerve damage including mechanical disruption of the normal neuronal architecture, delamination to fragmentation of the myelin sheath and marked cellular infiltration.

Finally, Iohom *et al.*[20] investigated the effects of intraneural injection on rats' sciatic nerve using 0.2 ml of ropivacaine 0.2 and 0.75%, compared with the same amount of saline. No distinction was made between intrafascicular or interfascicular injections. For each concentration and type of local anesthetic or saline, a total of 13 injections were conducted after surgical exposure of the sciatic nerve. During the follow-up period between 1 and 67 days, sciatic nerve function based on track analysis in combination with light microscopical examination were performed. Animals treated with saline, ropivacaine 0.2 and 0.75% had no detectable impairment of motor function. In addition, insignificant histological changes were seen in the ropivacaine and saline group.

Statistical analysis

The number of studies using comparable methodology is limited. Due to the heterogeneity of the available studies, it is not possible to combine all results. However, common factors such as intrafascicular or interfascicular injection, injection of a local anesthetic compared with saline, or injection pressure are presented in 2 or more studies.

Table 3. Calculated rates of risks of neurological deficit for the given etiological factor

	Etiologic factor	Incidence*	RR (95% CI)	Heterogeneity (Q value [I^2])
Selander *et al.* Gentili *et al.* Hadzic *et al.* Kapur *et al.*	Intrafascicular injection	62.7%	62.9 (13.1 - 303.2)	4.39 [54%]; P = 0.11
Hadzic *et al.* Kapur *et al.*	High injection pressure	100%	32.4 (4.8 - 218.6)	0.20 [0%]; P = 0.66

** Absolute risk of neurological deficit; RR, risk ratio; CI, confidence interval*

The results of all animal studies suggest that intrafascicular injection of local anesthetic carries the highest risk of transient neurologic deficit (Table 4). The percentage (absolute risk) of neurologic deficit is 62.7% (146/233) with RR of 62.9 (95% CI; 13.1 − 303.2). Comparison of injection pressure based on 2 studies[3,20] shows a significant relation between high injection pressure and nerve damage, with an RR of 32.4 (95% CI; 4.8 − 218.6). The incidence of high injection pressure (≥ 20 PSI) in the presence of intrafascicular injection is 44% (12/27).

Discussion

Our observations from animal studies suggest that intrafascicular injection is associated with a high incidence of nerve damage. Injection between the peri- and endoneurium (intrafascicular) seems to be frequently related with high injection pressure. This setting may lead to increased risk of nerve damage. In contrast, administration of local anesthetics in the interfascicular region does not necessarily lead to increased risk of nerve damage. Human and experimental studies suggest that drug injection at this location does not necessitate high injection pressure. These conclusions along with their level of evidence are summarized in table 4.

Our observations from the three human studies suggest that intraneural injection visualized by ultrasound may not increase the long-term risk of nerve damage. A slightly higher risk (< 4%) of transient neurologic dysfunction (< 3 weeks) is associated with ultrasound-detected intraneural injection. However, in light of the provided evidence,[24] *e.g.,* surgical incision side, incidence of nerve injury after high-risk surgery and the discrepancy between blocked nerved and area of numbness, it seems more likely that the observed transient neurologic dysfunction was attributed to the surgery rather than the nerve block.

Although there is a limited number of contemporary large scale studies examining the relation between nerve damage and intraneural injection available for review, there are none available for historical comparison with our present findings. The studies of Selander *et al.* in the 1980*s* have long been recognized as major source of evidence.[22,25] Although a wide spectrum of various concentrations of local anesthetics was tested against saline, a major drawback is the lack of comparison between intrafascicular and interfascicular injection. A second major source is the work of Gentilli *et al.* who investigated numerous types of local anesthetics and other agents in combination with either intrafascicular or interfascicular injection.[19] In addition, neurologic deficit after intraneural injection is reported for various agents other than local anesthetics.[26-28]

The pathophysiology of nerve damage after intrafascicular injection of local anesthetics

can be classified into morphological and structural damage to the nerve fibers, toxicity and nerve barrier dysfunction, and neural ischemia. The extent of each of these aspects is dependent on the mode of application, type, amount and concentration of local anesthetic and the equipment. In this respect, structural damage to the nerve fibers caused by the needle appears to be limited. Findings from a recent investigation in which only 3% of fascicles were damaged after intraneural needle insertion into the sciatic nerve, seem to confirm these observations.[29] Both internal composition of the nerves and the protective barrier of nonneural tissue around the nerve fascicles,[17,30,31] and the mechanically tough and resistant perineurium (in contrast to epineurium) are thought to hinder direct structural damage of the fascicles. In contrast, toxicity and neural ischemia are assumed to play a more important role in the etiology of nerve damage.[32] Although most local anesthetics administrated in clinical concentrations and doses do not cause nerve damage, prolonged exposure , high doses and high concentrations of local anesthetics have been surmised to result in neurologic deficit. However, clinical studies do not support these hypothesis as continuous infusion catheters are routinely used without neurologic complications. Moreover, direct intrafascicular injection of local anesthetics will potentiate the neurotoxic effect of higher concentrations of local anesthetics as well as harmful effect of added vasoconstrictors. In addition, a reduction of nerve blood supply caused by high intrafascicular pressure may result in neural ischemia. Intrafascicular injection of volumes as small as 50-100 μl may generate pressures that exceed capillary perfusion pressure for as long as 10 minutes and thus may cause ischemia.[33]

Injection requiring high pressure are likely to increase the risk of nerve damage because it may indicate drug administration in a noncompliant space. The definition of high injection pressure is not uniform as in one study, high pressure was defined as equal to or higher than 20 PSI,[21] while ≥ 25 PSI was used in another study (both studies are from the same group).[3] The risks of nerve damage might change if unified cut-off levels were used. Further, it is unknown if the observed nerve damage is persistent after one week. Clinical evidence suggests that neurologic dysfunction is generally transient and may last only for a couple of weeks.[1] In addition, findings of another included study in this review suggests that regeneration of the nerve fibers is possible after a relatively long period (67 days), even after injection of formalin 3%.[19] With a follow-up period of only 1 week, it is unclear whether the observed microscopic and functional deficit remain persistent.

A key limitation among animal studies is the reliable distinction between the position of the needle tip being intrafascicular (inside the perineurium) or outside of it. The fascicles inside the nerve are embedded in the nonneural tissue that is not visible from outside. Even with the use of light microscopy, reliable distinction of individual fascicles is still hampered due to the relative impenetrability of light by adipose tissue. Also, intrafascicular position of the needle derived by high injection pressure has its limitations. First, it is not known whether high injection pressure is actually caused by the dense structure of the fascicle, or by the needle tip being next to the perineural layer. Because the perineurium is a tough and mechanically resistant tissue, it is possible that the targeted perineurium is not punctured and the needle tip is placed against the layer that cause high injection pressures during injection. This uncertainty in the position of the needle may lead to inaccurate findings and conclusions. In addition, if not mechanically fixed during injection, small microscopic manipulation of the needle during injection causes displacement of the needle tip from *intrafascicular* to *interfascicular* area and are also leading to unreliable findings.

Table 4. Overview of the conclusions of the relation between intraneural injection and nerve damage.

Controls	Level of evidence
Intrafascicular injection is highly associated with (transient) nerve damage	Grade I
Interfascicular injection does not necessarily increase the risk of nerve damage	Grade I
High injection pressure is highly associated with nerve damage	Grade IIA
Intraneural injection of large amount of local anesthetics with high concentration may increase the risk of nerve damage	Grade IIB

Second, it is unclear whether nerve damage would still be observed after intraneural, high pressure injection of a control fluid. The possibility exists that intraneural injection of saline under high pressure, will not lead to nerve damage. Therefore, more studies dealing with intraneural injection, high injection pressure and nerve damage are warranted including reliable assessment of the position of the needle. The effect of saline with continuous pressure measurement of the peri- and endoneurium space is also needed.

In human studies, ultrasound was applied to capture intraneural injection. Although technical improvements has led to superior images in ultrasonography, its resolution is still insufficient to capture detailed overviews of the inner architecture of the nerves. While it is relatively easy to differentiate between intraneural and extraneural environment,[13] it is hard to distinguish between intrafascicular and interfascicular region. Thus, most ultrasound-guided clinical studies report problems with obtaining satisfactory nerve images in some of their patients.[34] Since a key issue in prevention of neurologic deficit in regional anesthesia is the accuracy and reliability of the equipment, future developments of ultrasonography should aim to improve its accuracy in reliably recognizing intrafascicular and interfascicular region.

The heterogeneity and quality of the available source studies included in this review calls for caution when interpreting the validity of our risk estimates. Differences in sample size, animal and human populations, type of local anesthetics, needles, methodologies and follow-up assessments undermine accurate comparisons of the relation between intraneural injection and neurologic complications reported in each study. Moreover, the presentation and assessment of complications related to intraneural injection is complex and inconsistent among studies, likely resulting in underreporting in some studies and over-reporting in others. For example, the presence of neurologic complications likely varied depending on the length of follow-up, blind assessment of histology and the accuracy of the tools such as ultrasound, manometers or light microscopy.

In summary, observations from animal studies suggest that intrafascicular injection may be associated with a high incidence of (transient) nerve damage; on the other hand interfascicular injection does not necessarily increase the risk of nerve damage; the need of high injection pressure seems to be associated with the occurrence of nerve damage, although no study was able to determine the exact position of the tip of the needle. Intraneural injection with high concentration may increase the risk of nerve damage.

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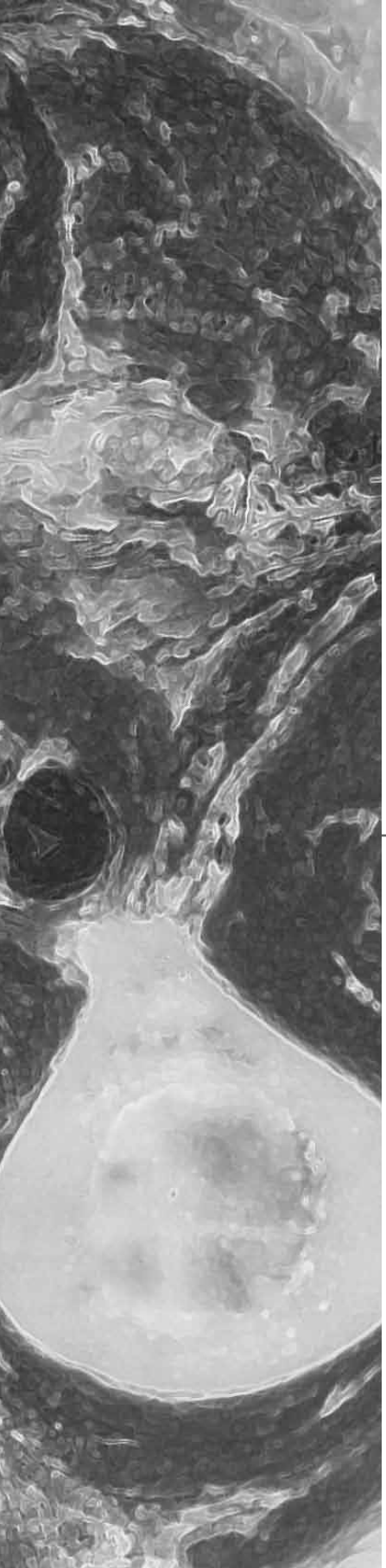

Chapter 7

Quantitative Architecture of the Brachial Plexus, Surrounding Compartments and Their Possible Significance for Plexus Blocks

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Abstract

Background **Nerve injury following regional anesthesia of the brachial plexus (BP) is a relatively rare and feared complication that is partly attributed to intraneural injection. However, recent studies have shown that intraneural injection does not invariably cause neural injury, which may be related to the architecture within the epineurium. A quantitative study of the neural components and the compartment outside BP was made.**

Methods **From four frozen shoulders high-resolution images of sagittal cross-sections with an interval of 0.078 millimeters were obtained using a cryomicrotome to maintain a relatively undisturbed anatomy. From this dataset cross-sections perpendicular to the axis of the BP were reconstructed in the interscalene, supraclavicular, mid-infraclavicular and subcoracoid regions. Surface areas of both intra-epineurial and connective tissue compartments outside the BP were delineated and measured.**

Results **The nonneural tissue (stroma and connective tissue) inside and outside the BP increased from proximal to distal, being significant between interscalene/supraclavicular and mid-infraclavicular/subcoracoid regions ($p < 0.001$ for tissue inside, $p < 0.02$ for tissue outside BP). The median amount of neural tissue remained about the same in the four measured regions (41.1 ± 6.3 mm^2, range 30 - 60 mm^2). The ratio neural:non-neural tissue inside the epineurium increased from 1:1 in the interscalene/supraclavicular to 1:2 in the mid-infraclavicular/subcoracoid regions.**

Conclusion **Marked differences in neural architecture and size of surrounding adipose tissue compartments are demonstrated between proximal and distal parts of the brachial plexus. These differences may explain why some injections within the epineurium do not result in neural injury and affect onset times of brachial plexus blocks.**

Nerve injury following regional anesthesia is a feared complication, which can cause immediate or sub-acute short-term neurologic deficits and pain sensations, which can last for weeks or even months.[1] Data about the incidence of nerve injury with the use of peripheral nerve blocks shows a relatively small incidence ranging from 0.02%[2,3] to 0.2%[4] for distal block (axillary nerve block) and 0.03%[3] to 0.4%[5] in short- and severe long-term neurologic complications of proximal blocks (interscalene nerve block). In animal studies, persistent neurologic complications range from 0 to 5% after brachial plexus blocks, depending on the technique used.[6] Intraneural injection of the local anesthetic is believed to be a mechanism, which might cause nerve injury, especially after intraneural injections that are associated with high pressures.[7] Therefore, the use of electrical neuro-stimulation to evoke motor responses in the proximity of the nerves without actually puncturing them has been advocated.

A further enhancement is the ultrasound-guided local anesthetic injection, which enables visualization of the individual brachial plexus constituents and is assumed to be more effective, less time consuming with potentially fewer complications.[8,9] Even with the precise visualization afforded by use of ultrasound most experts recommend avoiding injection within the epineurium.[10] However, recent findings about ultrasound guided axillary block with visually confirmed intra-epineurial injection of the local anesthetic showed that it does not invariably cause neural injury.[11] In fact, there were no long-term neurological deficits. This raises questions about the architecture of the brachial plexus within the epineurium and how variations in this architecture might explain how injections within the epineurium do not invariably lead to neural injury. Further knowledge of the physical amount of neural tissue and its ratio to non-neural tissue inside the epineurium would, therefore, provide new insights.

Furthermore, differences in neural architecture might shed some light on differences in onset time and local anesthetic volumes that exist in daily practice between proximal and distal brachial plexus blocks. A successful block of the upper extremity depends, among others, on the type, amount, concentration, lipophilicity, place of injection and anatomic distribution of the local anesthetic and of the lipid content of the nerve tissue and surrounding extraneural tissue. In general, proximal blocks (interscalene and supraclavicular) are thought to have a faster onset than distal blocks (infraclavicular and axillary), but there is little data or consensus. Further, it is difficult to compare proximal and distal techniques because nervous structures are blocked that differ in organization and topographical arrangement.

We hypothesized that distal compartments surrounding the brachial plexus are larger and contain more fat and stroma within the epineurium in the brachial plexus. This architecture would lead to a potentially larger volume of distribution in the distal sites for any local anesthetic injected. To evaluate this hypothesis, we determined the size of the compartments surrounding the brachial plexus at the sites mentioned above in human cadavers. Quantitative data of the brachial plexus based upon high-resolution cross-sectional images[12] were acquired in four regions: interscalene, supraclavicular, infraclavicular and subcoracoid.

Materials and methods

Cryomicrotomy was employed as it allowed us to conduct a detailed histologic examination while preserving the original relatively undisturbed neurovascular topography

Table 1. Baseline characteristics of the cadavers

Specimen	Age	Gender	Weight (kg)	Height (cm)	BMI*
L I, R I	62	female	73	168	25.9
R II	45	female	85	178	26.8
R III	73	male	92	188	26.0

* Body Mass Index; R: right specimen; L: left specimen

of the brachial plexus.[12] Advantages of this method are that dimensions and surfaces can be measured and that topographical relations remain unaltered, which is not the case when dissection is used.[12] Further, cryomicrotomy would provide a better insight in the dimensions and location of the various tissues that are bypassed when inserting a needle. This was combined with high-resolution photography.

After Institutional Review Board approval (University Medical Center Utrecht, Utrecht, the Netherlands) four shoulders of three different cadavers (Table 1) were obtained from the Department of Functional Anatomy of the University Medical Center Utrecht, Utrecht, the Netherlands. The shoulders contained the regions between the scalene muscles and the coracoid process. The shoulders were frozen in carboxymethylcellulose gel at minus 25 degree Celsius. Using a heavy-duty sledge cryomicrotome (PMV 450, LKB Instruments, Stockholm Sweden) consecutive sagittal 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 pixel/inch. The exact dimensions of the part of the specimen that appeared on the photographed image were noted. In total 1100-1500 images per specimen were collected. Thereafter, the coronal and axial 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). Thus, per shoulder, three digital datasets were obtained, each set comprising 8.8 gigabytes. Via synchronous display of all planes using an Interactive Image Sequence Viewer program (Moayeri N, Groen GJ, Utrecht, The Netherlands)[13] and E-MAC®, the individual roots, trunks, cords and nerves were visualized and identified. Synchronous refers to a feature of both programs to run movie-like animations of consecutive images in one of the planes, whereas, at the same time, the level of the section is shown as a moving line in the two other planes.

In each digital dataset of the shoulder, the interscalene, supraclavicular, mid-infraclavicular and the subcoracoid regions were documented. Per region five locations were chosen, a center site, i.e. midpoint, and locations 5 and 10 mm medial and lateral to each midpoint. If clear identification was not possible in the sagittal images, concomitant views of the brachial plexus in the two other planes were used to visualize and indicate the exact location and anatomy. In the interscalene region the midpoint was the first sagittal image where the trunks of the brachial plexus emerged between the anterior and middle scalene muscles. As midpoint of the supraclavicular region the site was chosen at which the brachial plexus lay immediately superior to the first rib. The mid-infraclavicular midpoint was the middle of the distance between the suprasternal notch and the most ventral part of the acromial apophysis. To identify this point during sectioning, a 22 G needle was inserted in the vertical plane, perpendicular to the back and just inferior to the clavicle. The needle was removed, the cannula was left *in situ* and the sagittal images containing the cannula formed

the midpoint. Finally, as midpoint of the subcoracoid region the most ventral point of the coracoid process was chosen. For each shoulder, in all 20 locations separate reconstructions of the brachial plexus were made strictly perpendicular to the axis of the plexus (figure 1A). Thus, a total of 80 digital perpendicular reconstructions were created. In each of the images, by using E-MAC®, the epineurial surface area was delineated after which pixel counting revealed the surface area in mm^2. 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. In the same manner, the individual neural fascicles with their perineurium were identified and their total surface area was calculated as neural tissue (figure 1B).

The borders of the tissue compartments surrounding the brachial plexus were identified using muscular borders or the first distinct fascial layer within the fat. In the interscalene region the borders were formed by the anterior and middle scalene muscles, in the subcoracoid region by the minor pectoral minor and subscapular muscles. In the supraclavicular and mid-infraclavicular regions, the first distinctive fascial layer outside the epineurial layer of the brachial plexus lay within a large mass of adipose tissue. The area within this connective tissue compartment was demarcated and calculated.

In each region, the surface areas of fascicles/nerves and epineurium were subtracted from each other. The medians and the standard deviations of all values in the same region (midpoint and 5 and 10 mm medial and lateral to the midpoint) in all shoulders were calculated including the areas surrounding the epineurium.

Some measurements were not included in the final analysis. The reason for this is that one or two regions medial or lateral to the midpoint in the interscalene and subcoracoid regions in the reconstructed perpendicular images did not contain the entire image of the brachial plexus. Differences in cross-sectional areas between the regions were determined by a two-sided student *t* test. For statistical significance, a value of $P < 0.05$ was chosen.

Results

Figure 2 shows each region of the brachial plexus in detail. All values below are presented as median ± SD, unless stated otherwise. The median amount of neural tissue remained about the same throughout the brachial plexus (41.1 ± 6.3 mm^2, range 30 - 60 mm^2) and did not show a significant difference between the four regions (figure 3A). The values for the interscalene, supraclavicular, mid-infraclavicular and subcoracoid regions respectively were 40.7 ± 3,8 mm^2 (range 32 - 45 mm^2), 45.0 ± 5.2 mm^2 (range 37 - 57 mm^2), 38.5 ± 4.4 mm^2 (range 33 - 48 mm^2) and 40.3 ± 9.4 mm^2 (range 30-60 mm^2). The non-neural tissue inside the epineurium increased from proximal to distal. The median surface areas were 46.7 ± 9.5 mm^2 (range 25 - 62 mm^2), 47.2 ± 7.4 mm^2 (range 36 - 64 mm^2), 75.4 ± 16.3 mm^2 (range 49 - 94 mm^2) and 76.0 ± 23.1 mm^2 (range 50 - 123 mm^2) for the interscalene, supraclavicular, mid-infraclavicular and subcoracoid regions, respectively. Differences in values between interscalene/supraclavicular and mid-infraclavicular/subcoracoid regions were significant ($P < 0.001$).

The ratio of neural to non-neural tissue in the epineurium is shown in figure 3B. In the interscalene, supraclavicular, mid-infraclavicular and subcoracoid regions the percentages of neural tissue inside the epineurium were, respectively, 45 ± 4% (range 41 - 57%), 48 ± 4% (range 42 - 58%), 34 ± 6% (range 29 - 48%) and 34 ± 3% (range 30-39%). These differences were significant ($P < 0.001$).

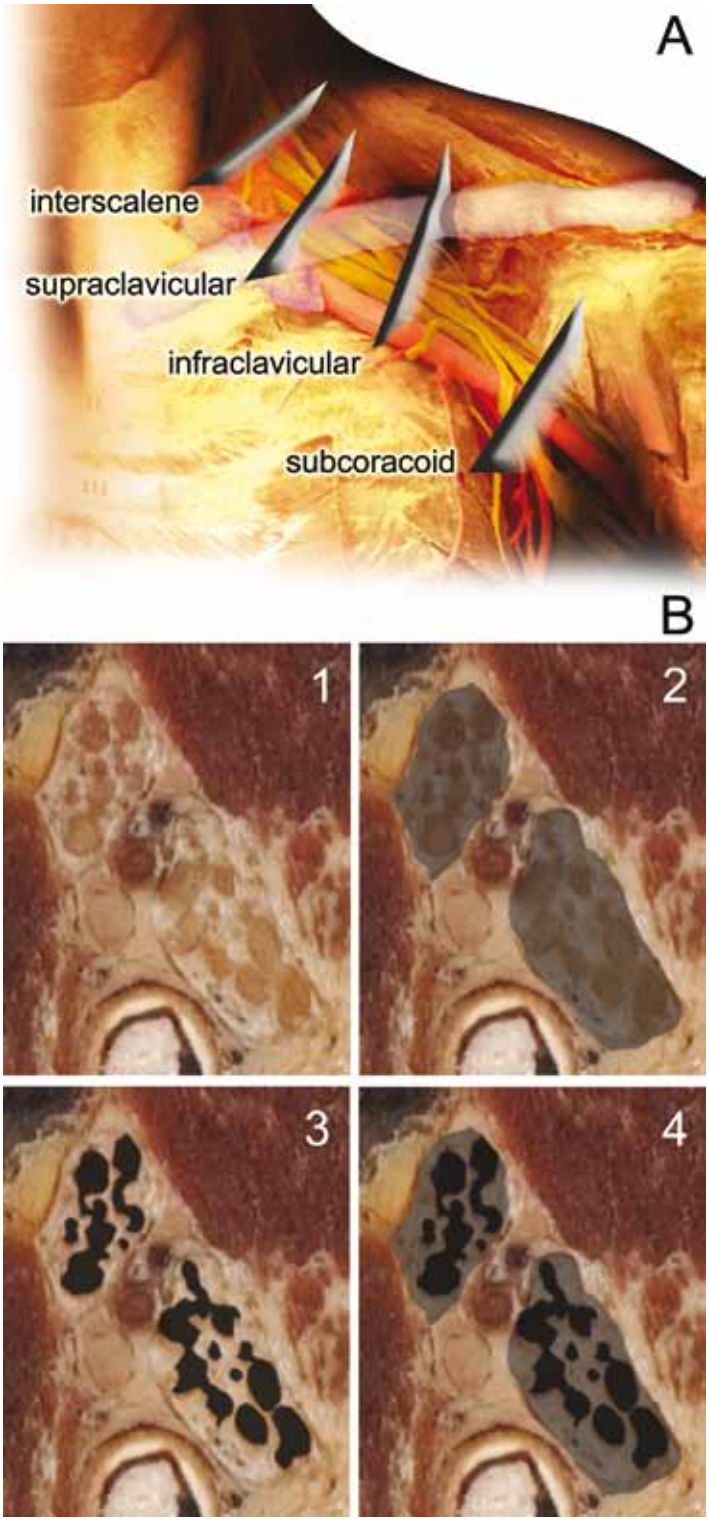

Figure 1.
A. Reconstructed image of the brachial plexus showing the interscalene, supraclavicular, mid-infraclavicular and subcoracoid regions.
B. Representative perpendicular reconstructions demonstrating how measurements were conducted.
(1) Original reconstructed image; (2) measured intra-epineurial tissue (shaded in grey); (3) measured neural tissue including perineurium and nerve fascicles (black spots); and (4) combined image showing both measurements superimposed on the same image.

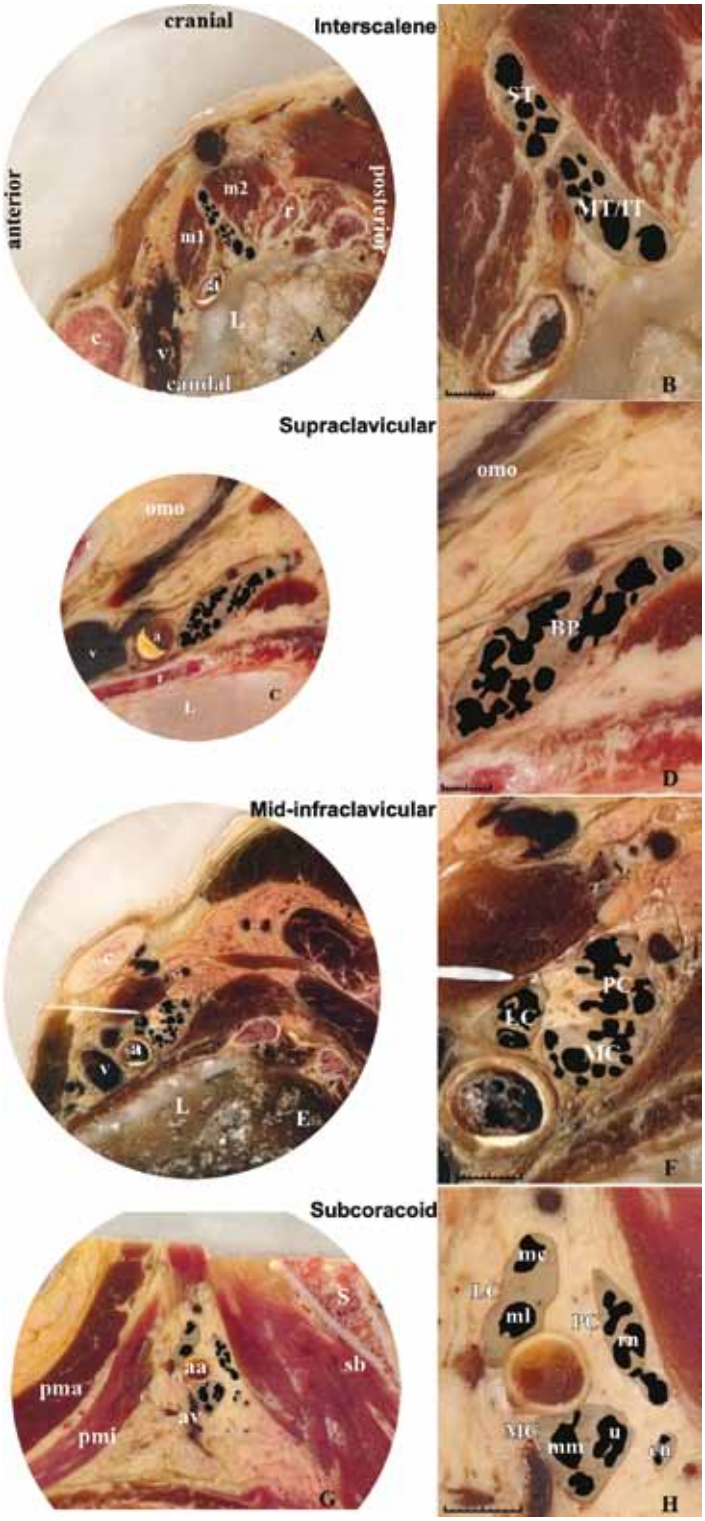

Figure 2.
Overview of the investigated areas (left column) with details of the measured neural contents (right column; black spots) and epineurial areas (grey fields).
A,B. Interscalene; **C,D.** supraclavicular; **E,F.** mid-infraclavicular; **G,H.** subcoracoid. *a/v* subclavian artery/vein; *aa/av* axillary artery/vein; *BP* brachial plexus; *c* clavicle; *cn* cutaneous nerves; *L* lung with plural cavity; *m1/m2* anterior/middle scalene muscle; *mc* musculocutaneous nerve; *ml/mm* lateral/medial root of median nerve; *ST/MT/IT* superior/middle/inferior trunk; *omo* omohyoid muscle; *PC/MC/LC* posterior/medial/lateral cord; *pma/pmi* major/minor pectoral muscle; *r* first rib; *rn* radial nerve; *S* scapula; *sb* subscapular muscle; *u* ulnar nerve. Bar represents 10 mm.

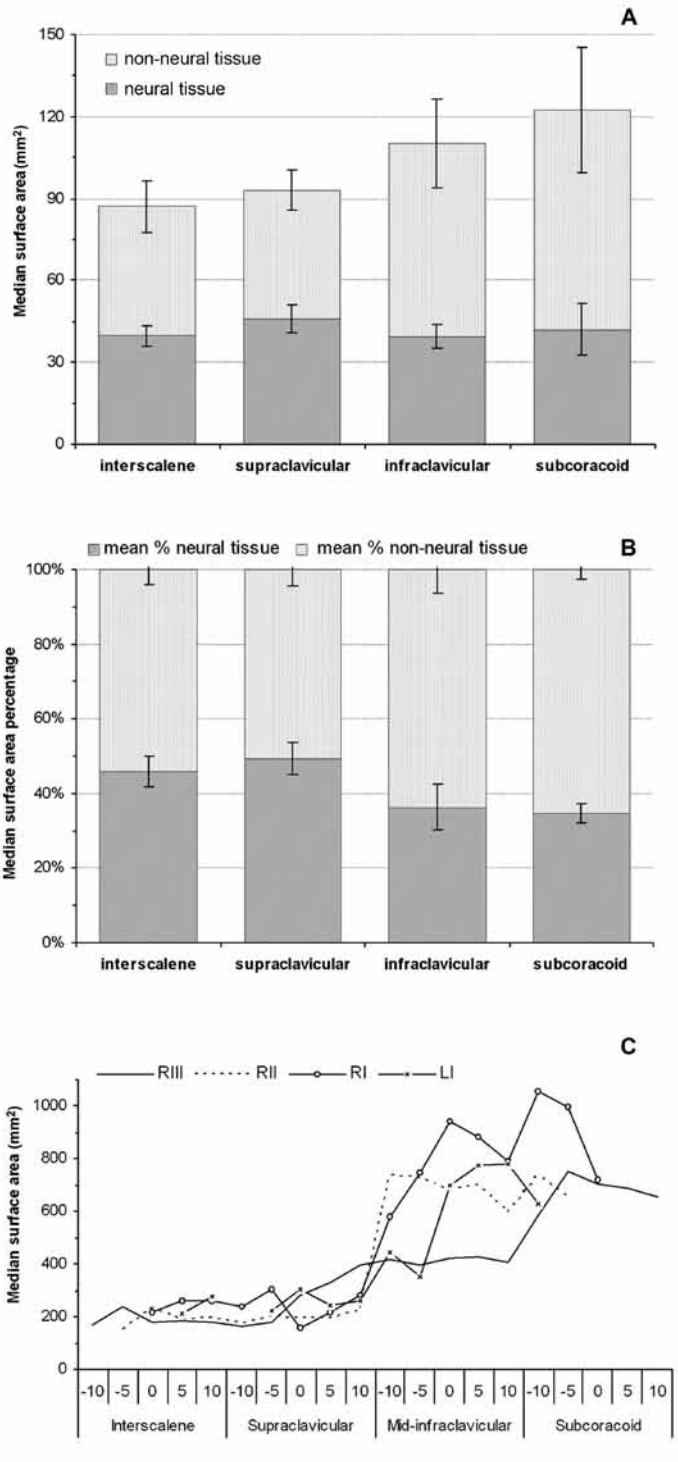

Figure 3. Measured areas in the interscalene, supraclavicular, mid-infraclavicular and subcoracoid regions of all shoulders (R: right; L: left). **A.** Absolute values (mm^2) of neural and non-neural (connective) tissue inside the epineurium (medians ± SD). **B.** Relative values (percentage) of neural versus non-neural tissue inside the epineurium (medians ± SD). **C.** Absolute values (mm^2) of adipose/connective tissue compartment surrounding the brachial plexus depicted per shoulder, from the most proximal (location -10 interscalene) to the most distal area (location +10 subcoracoid).

The area of the connective tissue compartment surrounding the brachial plexus increased in all shoulders from proximal to distal (figure 3C). The values per region showed the same pattern. The areas increased from 201.5 ± 38.5 mm^2 (range 152 - 275 mm^2), to 222.7 ± 63.33 mm^2 (range 159 - 396 mm^2), to 689.6 ± 181.7 mm^2 (range 354 - 946 mm^2) and 706.3 ± 148.4 mm^2 (range, 587 - 1058 mm^2) for the interscalene, supraclavicular, mid-infraclavicular and subcoracoid regions, respectively. The increase in area between interscalene/supraclavicular and mid-infraclavicular/subcoracoid regions showed a significant difference ($P < 0.02$).

Discussion

The present study demonstrates in relatively undisturbed anatomy that differences exist in neural architecture between the various parts of the brachial plexus, which may have implications for the understanding of the plexus blocks. The cryomicrotome technique we used is considered as the gold standard for allowing histologic examination of large areas of relatively undisturbed anatomy. It provides detailed information, which is at present superior to that of computed tomography, magnetic resonance imaging or ultrasound.[12,14] Furthermore, the high-resolution images and reconstructions we made with an interval less than 0.1 mm allowed us to accurately demarcate and measure the contents of the brachial plexus within and outside the epineurium.

The neural tissue inside the epineurium is formed by single nerve fibers enveloped by endoneurium, which are organized in bundles (fascicles) surrounded by perineurium. Although the perineurium *per se* is connective tissue as well, in this study we consider the perineurial tissue and its contents equivalent to neural tissue. The proximal (interscalene and supraclavicular) regions show a more solid, oligo-fascicular pattern. More distal, the fascicles show a more "scattered", polyfascicular pattern, which is in keeping with the work of Bonnel and Rabischong, who showed, from proximal to distal, an increase in the number of fascicles and decrease in diameter of fascicles.[15,16] Since the perineurium, in contrast to the epineurium, is a tough and mechanically resistant tissue,[17] it is unlikely that a blunt needle will penetrate it easily. These findings may explain why penetration of the epineurial layer does not always lead to an observed neural damage.[11] It can further explain that, when a needle hits the perineurium, paresthesias are elicited, and disappear after a very small redirection of the needle. The polyfascicular configuration and relative increase in non-neural tissue more distally may explain why these events occur without clinical neurological sequelae. Although results from two recent reports did show a higher incidence of neurological dysfunction in proximal versus distal nerve blocks, the absolute number of complications is too low to draw definite conclusions on its etiology.[3,18]

Injection inside the perineurium is associated with high injection pressures and leads to fascicular injury and neurological deficit, whereas injection inside the epineurium results in low initial pressures with return of normal motor function.[7] Further support for this phenomenon are the results from a recent study in rats, in which intraneural injections of ropivacaine at concentrations routinely used in clinical practice appeared to have no deleterious effect on sciatic nerve motor function.[19] Thus it is tempting to say, that an intraneural injection will not invariably cause neural damage, as long as one stays out of the perineurium.

The neural tissue content of the brachial plexus remained about the same throughout the plexus. It varied between 38.5 - 45 mm^2, but the ratio of neural : non-neural tissue decreased from a proximal value (interscalene/supraclavicular) of about 1:1 to a distal value (mid-infraclavicular/subcoracoid) of about 1:2. Our data confirms that of earlier histological

studies of 21 dissected brachial plexuses.[15,16] The 2:1 ratio we found is in keeping with these studies,[15,16] but also with the work of Slingluff *et al.*[20] However, the absolute and relative increase in non-neural tissue from the proximal (interscalene) to the distal (subcoracoid) parts of the plexus is not in keeping with that recent report.[20] In that dissection study the amount of non-neural tissue remained about the same, and in fact showed a slight decline from proximal to distal (67% to 65.4%).[20] The observed differences in the proximal parts are most probably explained by the differences in techniques used, i.e. undisturbed anatomy versus dissection. Furthermore, also the size of the compartment of adipose tissue outside the epineurium increased between interscalene and subcoracoid regions.

We speculate that the anatomic findings we described may have correlations with the onset time of brachial plexus blocks. Most practitioners attempt to inject local anesthetic outside the epineurium when they perform brachial plexus anesthesia. We have shown that there is a larger mass of fat outside the plexus in the more distal regions of the plexus, which might serve as a reservoir for lipophilic local anesthetics. Thus, the time needed to reach the neural tissue might be prolonged since less local anesthetic is available to diffuse across the epineurium to block the neural tissue. At the same time, from proximal to distal, the neural tissue is surrounded by an increasing amount of epineurial connective tissue. Thus, the local anesthetic will physically need more time to reach the fascicles if it is not injected in the vicinity of the fascicles. Also, the diffusion rate of the connective tissue will differ if it contains different substances. The afore-mentioned factors would lead to a slower onset time and a requirement for larger doses of local anesthetic in the distal plexus. This is, in fact, what most practitioners observe in clinical practice. Unfortunately, no clinical studies have appeared up to now comparing onset time of the same local anesthetic between proximal and distal brachial plexus blocks. Since we did not include injection of stained solutions in cadavers or study the spread of local anesthetics in patients, these assumptions need to be confirmed in further studies. Finally, one should take into account that, the minimal local anesthetic concentrations commonly used to achieve reliable block require up to 40 ml of injected local anesthetic. This large dose, may mask the differences, which could be expected between proximal and distal approaches to the brachial plexus.

The limitations of this study make it necessary to use caution in extrapolating the data to the clinical field. The number of specimens used is very small, partly because of the very elaborate work in obtaining, processing and reconstruction of the large amount of images. However, in our opinion, the data appears to be reliable since no large differences in measured values were observed between the specimens and since the observed increments appeared in all. The present study also does not take into account the elasticity of tissue in living patients. In ultrasound studies, an expansion of the epineurium of the brachial plexus components is observed after local anesthetic injection inside the epineurial layer.[11] Further studies using the same manner of analysis after injection of stained solutions in the four brachial plexus approaches are recommended, as well as clinical imaging studies with local anesthetics to confirm our findings *in vivo*.

In conclusion, in relatively undisturbed anatomy using cryomicrotomy differences in neural architecture and size of surrounding adipose tissue compartments have been demonstrated between proximal and distal parts of the brachial plexus. The observed differences may explain why injections within the epineurium do not always result in neural injury and may also be a factor in determining the onset time and quality of blocks performed at different levels along the course of the brachial plexus.

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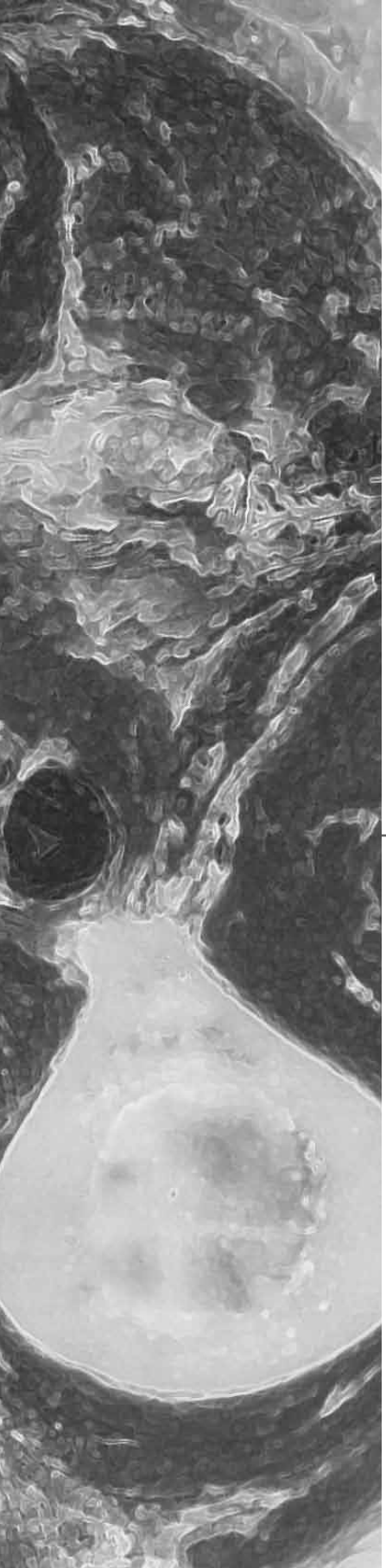

Chapter 8

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

Nizar Moayeri & Gerbrand J. Groen

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Abstract

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 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. We aim 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 cryomicrotome, consecutive transversal sections (interval, 78 μm) were obtained and photographed. Reconstructions of SN were made strictly perpendicular to its long axis in 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 of SN decreased significantly towards distal (midfemoral/popliteal region) ($p < 0.001$). The relative percentage of neural tissue (mean, ± SD) decreased from midgluteal (67% ± 7%), to subgluteal (57% ± 9%), to midfemoral (46% ± 10%), to popliteal (46% ± 11%). Outside the sciatic nerve, the fat and connective tissue compartment increased significantly between proximal and distal.**

Conclusion **In sciatic nerve, the ratio neural:nonneural tissue changes significantly from 2:1 (mid- and subgluteal) to 1:1 (midfemoral and popliteal). This suggests a higher vulnerability for neurological sequelae in the proximal sciatic nerve, and may explain differences observed in minimum effective anesthetic volume and onset time between proximal and distal sciatic nerve 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 injection pressure, and direct mechanical injury have been postulated as possible contributers.[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 micro-architecture of the peripheral nerve. In an earlier study, the authors have shown that the distribution of neural to nonneural tissue inside the epineurium changes 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 increases from 1:1 proximal to 1:2 distal towards the shoulder. In addition, towards 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 more nerve injuries are seen in the proximal brachial plexus (interscalene) blocks compared with the 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 towards 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 adipose and connective tissue surrounding the sciatic nerve was determined.

Methods

After Institutional Review Board approval (University Medical Center Utrecht, Utrecht, the Netherlands) five upper legs of five different cadavers (Table 1) were obtained from the Department of Anatomy of the University Medical Center Utrecht, Utrecht, the Netherlands. The investigated cadavers did not have any known comorbidities affecting their nerves. The investigated cadavers did not have any 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 minus 30 degrees Celsius. 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 pixel/inch. The exact dimensions of the part of the specimen that appeared on the photographed image were noted. In total, 8000-9600 images per specimen

Table 1. Baseline characteristics of the cadavers

Specimen	Age	Gender	Weight (kg)	Height (cm)	BMI*
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

* Body Mass Index; R: right specimen; L: left 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 (Figure 1A). In the midgluteal region, the midpoint was the first reconstructed image where the sciatic nerve emerged inferior to the piriformis. As 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 prior to sectioning. Finally, as 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. Thus, a total of 100 digital perpendicular reconstructions were created. In each of the reconstructed images, the epineurial surface area was delineated and measured using public domain Java image processing program *ImageJ 1.40g* (Rasband W., National Institute of Mental Health, 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 mm^2 and defined as neural tissue (Figure 1B). The remaining surface area within the sciatic nerve was defined as nonneural tissue and calculated by subtracting the total surface area of the fascicles from the total surface area of the epineurium.

The borders of the tissue compartments surrounding the sciatic nerve were identified using muscular borders and fascial layers (Figure 2). In the midgluteal region (Figure 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 (Figure 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 (Figure 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.

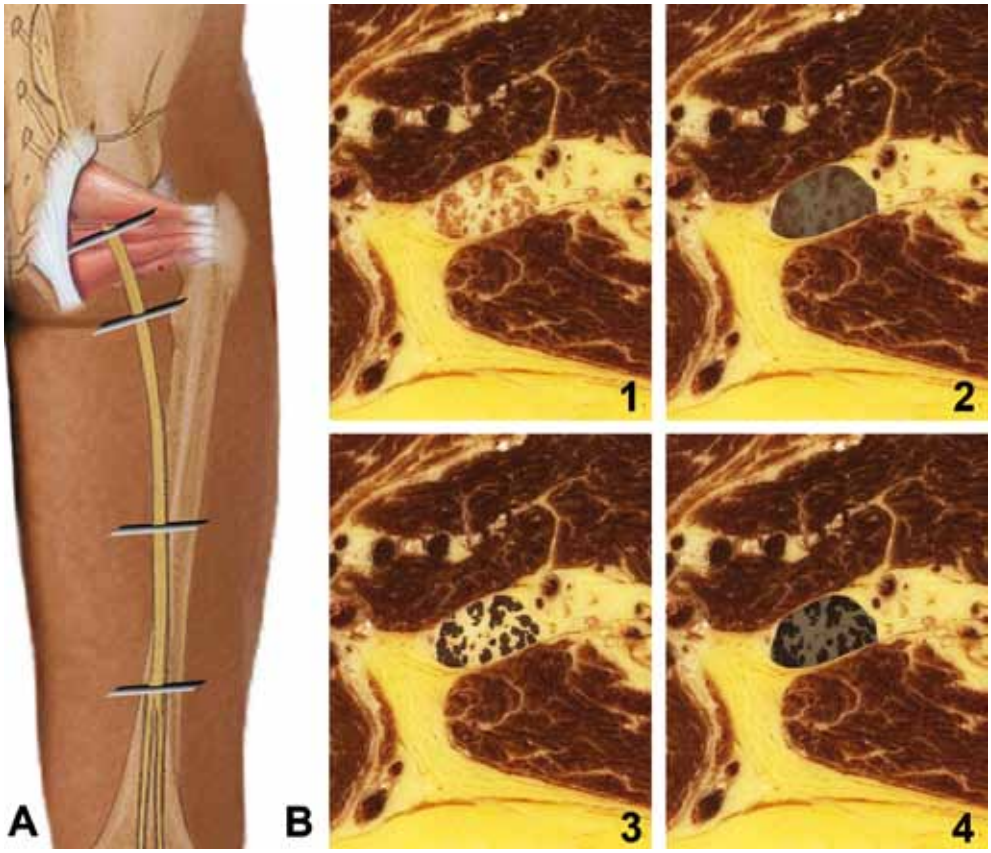

Figure 1. (A) Schematic diagram showing the location of midgluteal, subgluteal, midfemoral and popliteal sciatic nerve. (B) Representative reconstructions perpendicular to the long axis of the sciatic nerve demonstrating how measurements were conducted. (1) Original image; (2) measured total epineurial tissue (shaded in grey); (3) measured neural tissue (perineurium and nerve fascicles; black dots); and (4) combined image showing both measurements superimposed.

Finally, in the popliteal region (Figure 2G), the borders 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 medius. The area within these adipose tissue compartments was demarcated and measured.

Statistical Analysis

In all specimens, the means ± standard deviation of all values in the same region (midpoint, 5 and 10 mm proximal, and 5 and 10 mm distal to the midpoint) were calculated. Thus, 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 ANOVA test, with Bonferroni correction. SPSS Statistics (version 17.0.0, SPSS Inc. Chicago, IL) was used for statistical analysis. For statistical significance, a value of $P < 0.05$ was chosen.

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				.004		*1,000*
vs.	Midfemoral				.000		.000
vs.	Popliteal				.000		.001
Subgluteal		33.9 ± 6.0	25.9 ± 5.3	56.7 ± 8.8		231 ± 57	
vs.	Midfemoral				.015		.000
vs.	Popliteal				.012		.023
Midfemoral		18.4 ± 3.8	22.6 ± 6.8	45.7 ± 9.6		87 ± 34	
vs.	Popliteal				*1.000*		.000
Popliteal		19.1 ± 4.0	23.7 ± 7.3	45.7 ± 10.9		320 ± 101	

All data are presented as mean ± SD. Bonferroni adjustment for multiple comparisons was 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).
*** Cross-sectional area of adipose tissue outside 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.
‡ Comparison of absolute amount of adipose tissue outside the sciatic between the regions.

Results

Figure 2 shows in detail reconstructed images of the sciatic nerve in the midgluteal, subgluteal, midfemoral and popliteal region. 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 ($p < 0.0001$) (Figure 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 region is significant ($p < 0.001$).

The percentage of neural tissue inside the epineurium of the sciatic nerve is shown in figure 3B. The highest percentage of 66.7% ± 6.5% was seen in the midgluteal region, whereas the lowest percentage is observed in both midfemoral and popliteal regions, around 46% ± 10%. The significant decrease of percentage ($p < 0.0001$) between the proximal and distal regions was not only due to an absolute decrease of neural tissue, but also to an increase of nonneural tissue compared to 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

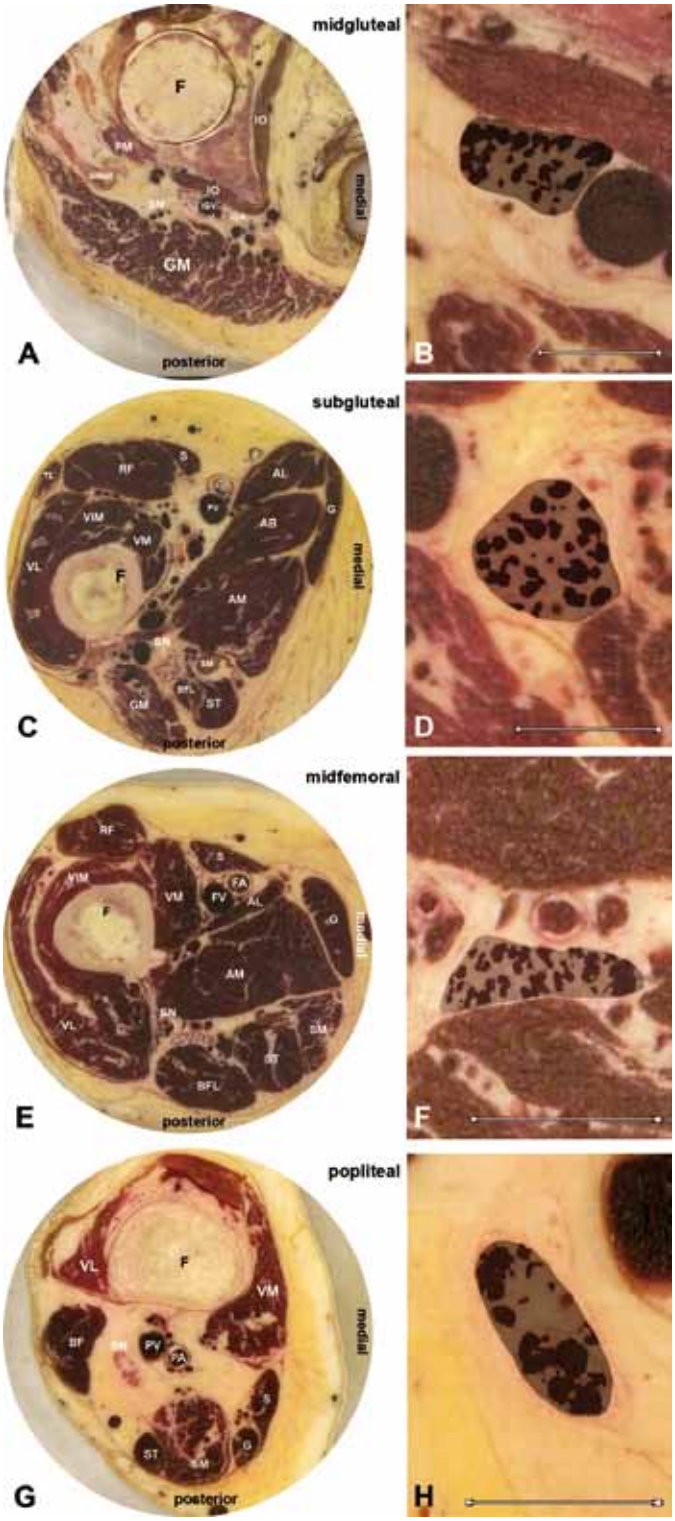

Figure 2. Overview of the investigated areas (left column) with details of the measured neural contents (right column; black dots) and epineurial areas (grey fields). (A,B) midgluteal; (C,D) subgluteal; (E,F) midfemoral; (G,H) popliteal.

AM/*AB*/*AL* adductor magnus/brevis/longus; *BF*/*BFL* biceps femoris long head; *F* femur; *FA*/*FV* femoral artery/vein; *G* Gracilis; *GM* gluteus maximus; *GMed* gluteus medius; *IGA*/*IGV* inferior gluteal artery/vein; *IO* internal obturator muscle; *PA*/*PV* popliteal artery/vein; *PM* piriformis; *RF* rectus femoris; *S* sartorius; *SM* semimembranosus; *SN* sciatic nerve; *ST* semitendinosus; *TL* tensor fascia latae; *VL*/*VIM*/*VM* vastus lateralis/intermedius/medius.
Bar = 10 mm.

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 (Figure 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 to 19 mm^2, respectively), whereas the nonneural tissue remained about the same (17 - 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 to 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 following 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% CI: 0.02 - 9.96), compared to 0.24% (95% CI: 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 neurological 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] Since the perineurium, in contrast to the epineurium, 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

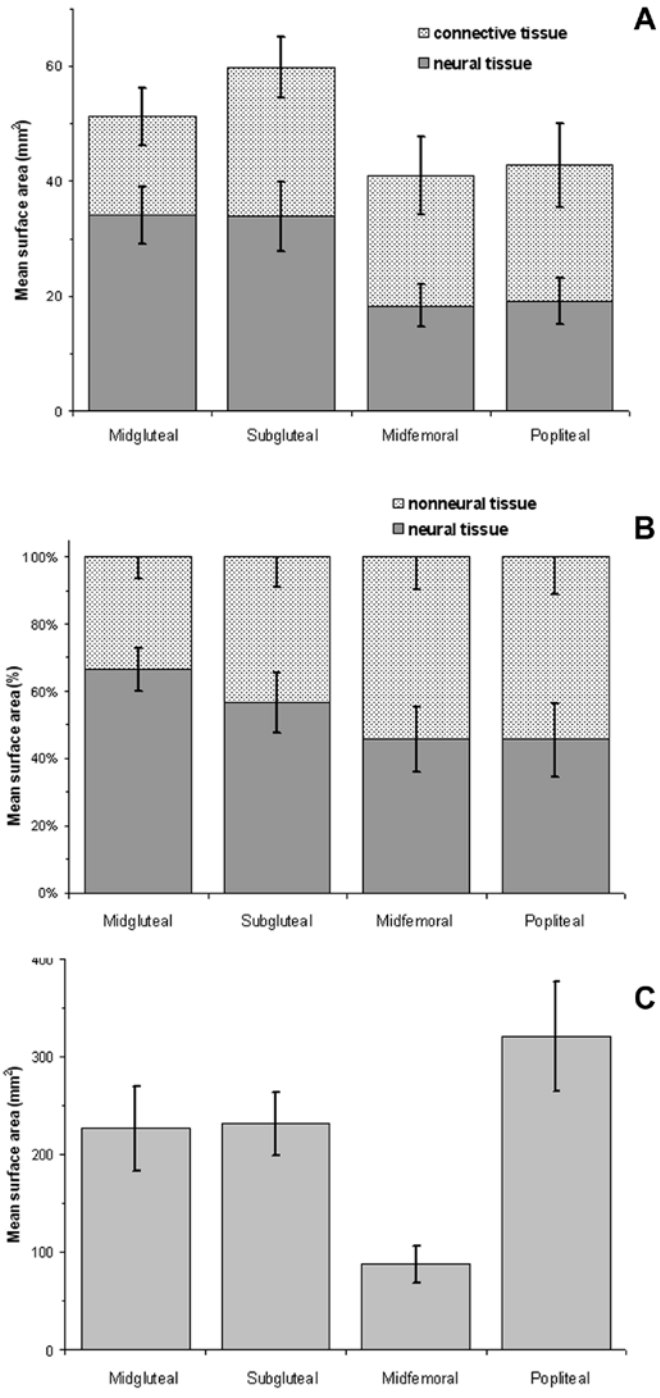

Figure 3. Measured areas in the midgluteal, subgluteal, midfemoral and popliteal regions of all upper legs. (A) Absolute values (mm^2) of neural and nonneural (connective) tissue inside the epineurium (means ± SD). (B) Relative values (percentages) of neural versus nonneural tissue inside the epineurium (means ± SD). (C) Absolute values (mm^2) of adipose/connective tissue compartment surrounding the sciatic nerve.

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 neurological sequelae. These include procedure-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 pre-existing 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.* reported a larger volume of local anesthetic for the popliteal sciatic nerve block compared to the subgluteal approach.[20] 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 to 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 to a more distal approach.[25] However, while Kilpatrick *et al.* reported a better success rate with the midgluteal approach compared to the popliteal approach (95% vs. 45% of patients; $p < 0.01$), no difference in onset time was noted.[26] 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.* found significantly shorter onset time of sensory block in the midfemoral group compared to the popliteal group.[27]

It appears 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 since 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 post-mortem examination and living individuals is impossible. The number of specimens used in our report is small, partly because of the very 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, since 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 appears to be reliable since 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 since it is considered the gold standard of 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 is 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 post-mortem 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 about 2% or less.[35]

In summary, in the sciatic nerve, the ratio of neural to nonneural tissue changes significantly from 2:1 (mid- and subgluteal) to 1:1 (midfemoral and popliteal). The findings would suggest a higher vulnerability for neurological 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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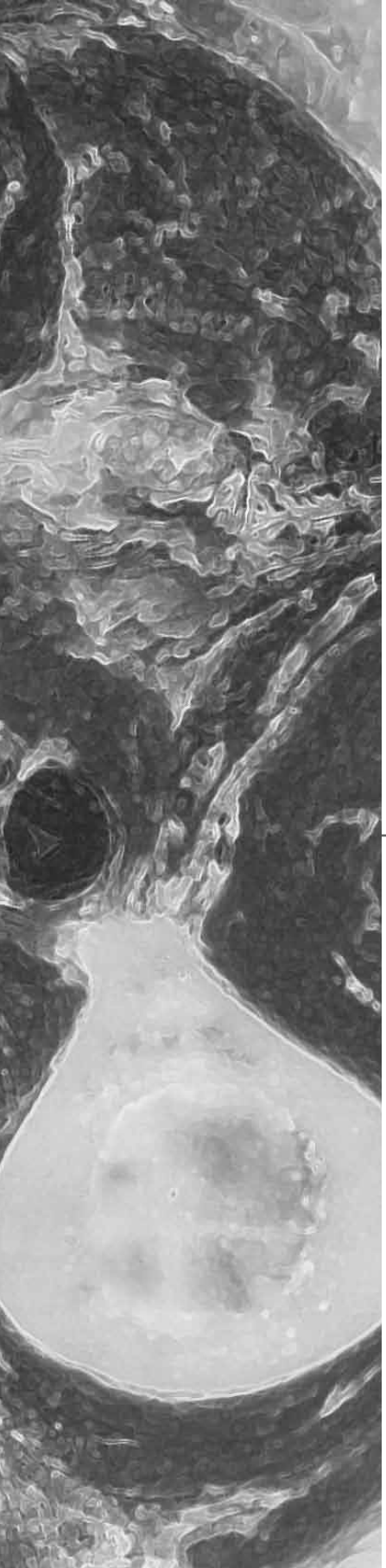

Chapter 9

Extraneural *vs.* Intraneural Stimulation Thresholds during Ultrasound-guided Supraclavicular Block

Paul E. Bigeleisen, Nizar Moayeri, Gerbrand J.Groen

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Abstract

Background **A stimulation current of no more than 0.5mA is regarded as safe in avoiding nerve injury and delivering adequate stimulus to provoke a motor response. However, there is no consistent level of stimulating threshold that reliably indicates intraneural placement of the needle. The authors determined the minimally required stimulation threshold to elicit a motor response outside and inside the most superficial part the brachial plexus during high-resolution, ultrasound-guided, supraclavicular block.**

Methods **After institutional review board approval, ultrasound-guided, supraclavicular block was performed on 55 patients. Patients with neurologic dysfunction were excluded. Criteria for extraneural and intraneural stimulation were defined and assessed by independent experts. To determine success rate and any residual neurologic deficit, qualitative sensory and motor examinations were performed before and after block placement. At 6 month follow-up, the patients were examined for any neurologic deficit.**

Results **Thirty-nine patients met all set stimulation criteria. Median ± SD (interquartile range) minimum stimulation threshold outside was 0.60 ± 0.37 mA (0.40, 1.0) and inside 0.30 ± 0.19 mA (0.20, 0.40). The difference of 0.30 mA was statistically significant ($P < 0.0001$). Stimulation currents of 0.2 mA or less were not observed outside the trunk in any patient. Significantly higher thresholds were observed in diabetic patients. Success rate was 100% after 20 min. Thirty-four patients had normal sensory and motor examination at 6 months. Five patients were lost to follow-up.**

Conclusion **Within the limitations of this study and the use of ultrasound, a simulation current of 0.2 mA or less is reliable to detect intraneural placement of the needle. Furthermore, stimulation currents of more than 0.2 and no more than 0.5 mA could not rule out intraneural position.**

Neurologic dysfunction is recognized as a rare but potential complication of regional anesthesia. A number of related factors such as obesity,[1] neurologic and metabolic diseases,[2-4] neurotoxicity,[5] and mechanical and ischemic injury may contribute to the development of acute and/or chronic nerve damage. Intrafascicular puncture and injection as well as high intraneural pressure during injection have also been postulated as potential etiologic factors.[6-10] Some authors recommend using an electrostimulation-guided technique to improve efficacy and decrease the risk of nerve puncture.[11] However, there is still controversy about the level of stimulating current required for a successful block at which the needle will remain a safe distance from the nerve to avoid injury.[12]

Current stimulation thresholds less than 0.5 mA have been recognized to deliver adequate stimulus to provoke a motor response while causing minimal discomfort to the patient.[13,14] However, stimulating currents less than 0.5 mA do not guarantee the proximity of the needle to the neural tissue.[15] Furthermore, animal studies have shown that in some cases with the needle intraneurally, a stimulation current of 0.5 mA or more was required to induce a contraction.[16,17] Recently, in pigs, specific responses to nerve stimulation with currents < 0.2 mA have been shown to occur only when the needle tip was positioned intraneurally, but reports on humans are lacking.[17]

We hypothesized that the level of stimulating threshold outside the nerve differs significantly from the level inside the nerve, and can be used to predict whether the needle tip is extraneural or intraneural. The position of the needle relative to the nerve was determined by ultrasound and criteria have been set to adequately identify and ensure needle-to-nerve contact. To test our hypothesis, we determined the minimally required stimulation threshold to elicit a motor response just outside and inside the most superficial part of the brachial plexus during high-resolution, ultrasound-guided, supraclavicular block.

Materials and Methods

Fifty-five consecutive patients (American Society of Anesthesiology physical status 1 to 3) who presented for wrist or hand surgery, were enrolled in the study after institutional review board approval (Linden Oaks Surgery Center, Rochester, NY), and written informed consent. Patients whose age was greater than 17 years were included in the study. Patients were excluded if the surgeon noted any sensory or motor abnormality in the neurologic examination of the patient's operative extremity. Demographic data including age, gender, weight, and height were recorded. Preexisting diabetes mellitus was also recorded. Relevant diabetic status included preexisting polyneuropathy defined as prediagnosed retinopathy or sensory or motor dysfunction of the lower limbs, insulin dependency, duration of disease after diagnosis, and fasting glucose and hemoglobin A1c level on admission.

Technique

A 22-gauge, 5-cm stimulating needle (B.Braun, Bethlehem, PA) attached to a nerve stimulator (model HNS 11, B.Braun) was used for all nerve blocks. All blocks were performed under ultrasound guidance using a L25 probe resonating at 13 MHz in the multibeam mode (MicroMaxx, Sonosite, Bothwell, WA) or a Terason Platform (Terason Ultrasound, Burlington, MA) using a L33 probe resonating at 12 MHz in the multibeam mode. Each block was recorded in real-time from the ultrasound device to a digital tape recorder (GV-

D900, Sony, San Diego, CA). At the same time, a nurse recorded the motion of the patient's operative extremity using a digital video camera (DCR PC1, Sony). After sedation with up to 2 mg of midazolam and 100 mcg of fentanyl, the brachial plexus was imaged in the supraclavicular fossa. The nerve stimulator frequency was set to 2 Hz, amplitude to 1.6 mA, and pulse width to 0.1 msec. Using a modified Plumb-Bob approach, the probe was placed in an oblique sagittal orientation in the supraclavicular fossa.[18]

Outside vs. Inside

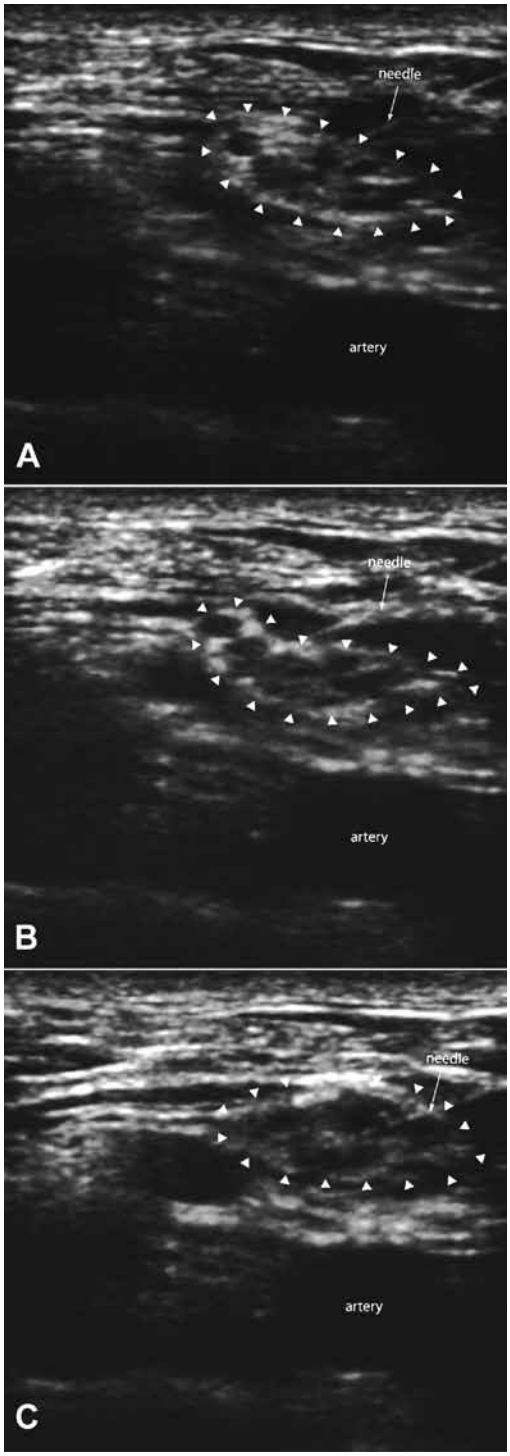
The interpretation of the data highly relies on the difference in location between outside and inside the nerve. The criteria for extraneural and intraneural needle tip location were defined as follows: (1) extraneural position (needle-to-nerve contact) when contact combined with slight indentation of the nerve wall was visualized by ultrasound,[19] and (2) intraneural position (needle-in-nerve) when the needle tip was visualized adjacent to the nerve fascicles, which appear as distinct round- to oval-shaped hypoechoic nodules,[20] followed by distension and expansion of the nerve after injection of a small amount of local anesthetic.[16,21-23]

The needle was inserted anterior to the probe and advanced in-line until the tip of the needle contacted the most superficial part the brachial plexus (Figure 1, A and B). After confirming the indentation of the nerve wall, the needle was drawn back just enough to undo the indentation, but still in contact with the nerve wall. If there was a motor response, the current was reduced to identify the threshold. If there was no motor response on contact, the current was increased until muscle twitches were observed, and threshold values were recorded. The needle was then advanced further into the confines of the trunk based on the intraneural criteria described earlier. The current amplitude was then decreased until the contraction vanished. The thresholds at which the contractions within the trunk vanished were recorded.

After recording the current threshold, intraneural position of the needle was further ascertained in all cases by injection of a maximum of 5 ml of local anesthetic (bupivacaine 2.5 mg/ml, lidocaine 10 mg/ml and epinephrine 3 mcg/ml) over approximately 15 seconds (Figure 1C). The needle was withdrawn immediately after confirmation of intraneural injection. Any injection, whether outside or inside the trunk was terminated when injection produced dysesthesia, or when the anesthesiologist felt unusually high resistance during attempted injection. With the stimulator turned off, after repositioning the needle, a total of 20 ml was injected around the deeper parts of the brachial plexus. All injections were performed by one staff anesthesiologist with experience in ultrasound-guided supraclavicular block. Only the stimulation thresholds of the initially stimulated superficial part of the brachial plexus were included for final analysis. (Video Supplemental Digital Content 1 demonstrates extraneural and intraneural needle tip position and injection, 60 seconds, 8 MB)

Image analysis

The video and ultrasound recordings of each patient were spliced together on the same time line after the completion of the block using Adobe Premiere software (Adobe, San Jose, CA). Each time line (video and ultrasound recording) was reviewed independently by the author performing the block as well as a licensed sonographer experienced in musculoskeletal



imaging and an anesthesiologist experienced in ultrasound-guided supraclavicular block. Only patients, who fulfilled all criteria of extraneural and intraneural stimulation, including the confirmation by all independent experts, were included in the study.

Patients

All patients had a sensory and motor neurologic examination 20 minutes after completion of the block. Sensory function of the dermatomes C5-T1 was tested with a sharp 25-gauge needle in the skin distribution areas of the musculocutaneous nerve (lateral forearm), the median nerve (palmar surface of the thumb and palmar tip of the middle finger), the radial nerve (dorsum of the wrist) and the ulnar nerve (palmar surface of the fifth finger). A score of 1 was given if the patient could identify pinprick and 0 if the patient had no sensation or only pressure sensation. The muscular examination was done using the Medical Research Council scale (5 = full strength, 0 = no movement) by asking the patient to perform the following maneuvers: elbow flexion (musculocutaneous nerve), flexion of the distal interphalangeal joint of the second finger (median nerve), extension of the wrist (radial nerve) and abduction of the third and fourth fingers (ulnar nerve).

All patients were called at home within 48 hours after the completion of the surgery to determine if they had any

Figure 1. Ultrasonographic overview of the neurovascular structures in the supraclavicular region; *artery: subclavian artery; arrowheads display the outer border of the brachial plexus*. **A.** Needle is against the wall of the brachial plexus. **B.** Needle is touching and indenting the wall of the plexus (needle-to-nerve contact). **C.** Intraneural injection after positioning the needle inside the plexus (needle-in-nerve).

Table 1. Absolute Value of Minimum Stimulation Current Required to Elicit Muscle Contraction

	All patients (n = 39)		Non-DM patients (n = 32)		DM patients (n = 7)	
Current (mA)	Out (%)	In (%)	Out (%)	In (%)	Out (%)	In (%)
≤ 0.2	0	14 (36%)	0	14 (44%)	0	0
> 0.2 - ≤ 0.5	16 (41%)	21 (54%)	16 (50%)	16 (50%)	0	5 (71%)
> 0.5 - ≤ 1.0	16 (41%)	4 (10 %)	13 (41%)	2 (6%)	3 (43%)	2 (29%)
> 1.0	7 (18%)	0	3 (9%)	0	4 (57%)	0

DM: diabetes mellitus; *Out:* outside the nerve; *In:* inside the nerve

persistent numbness, or weakness, or pain in the surgical extremity or the site of injection. All patients were seen by the surgeon within 72 hours of completion of the surgery, at 3 weeks, and by the surgeon or her physician's assistant at 6 months. All patients had a neurologic examination by the surgeon or her assistant at 72 hours, 3 weeks, and at 6 months.

Statistical analysis

Data are presented as median ± SD and interquartile range (IQR; 25%, 75%). Statistical significance of the difference in stimulation thresholds between inside and outside the trunk was performed using a two-tailed Wilcoxon signed-rank test. Analysis of differences between diabetic and nondiabetic patients was done using a Mann-Whitney U test. $P < 0.05$ were considered statistically significant. All the statistical analyses were performed using XLSTAT-Pro statistical software package (version 2007, Addinsoft, New York, NY).

Results

Thirty-nine patients (25 woman, 14 men) met all criteria of stimulation for outside and inside the nerve, including complete agreement of the independent experts. Their median age and body mass index (BMI) were 54 ± 17.6 yr (range, 18 – 83 yr), and 29.5 ± 4.2 kg/m^2 (range, 21.0 – 37.9 kg/m^2), respectively. Sixteen patients did not fulfill the inclusion criteria and were excluded. In all these patients, some local anesthetic needed to be injected to identify the position of the needle tip before stimulation. The median age and BMI of the excluded patients were 59.5 ± 18.6 yr (range, 19 – 81), and 33.6 ± 3.7 kg/m^2 (range, 25.7 – 40.9 kg/m^2), respectively. A significantly higher BMI was measured in the excluded patients compared to the included patients ($p < 0.001$).

The median ± SD (IQR) stimulation threshold *outside* the trunk was 0.60 ±0.37 mA (0.40, 1.0) compared to a value *inside* the trunk of 0.30 ±0.19 mA (0.2, 0.4) (Figure 2). Table 1 shows the distribution of the stimulation thresholds categorized in four groups, *i.e.,* less than or equal to 0.2 mA, between 0.20 and 0.5 mA, between 0.50 and 1.0 mA, and more than 1.0 mA. Stimulation currents less than or equal to 0.2 mA were not observed outside the trunk in any patient. In 10% of patients, the stimulating threshold within the trunk exceeded 0.5 mA. Figure 3 illustrates the difference between the stimulating thresholds outside and inside the nerve for each individual patient. In 87% of patients, the stimulation threshold necessary to achieve a contraction decreased. In the remaining 5 patients the stimulation threshold remained the same. In these patients, a value of 0.4 mA was measured in four patients and a value of 0.3 mA in one patient for both outside and inside the trunk. Twenty-four patients (61%) experienced a difference greater than or equal to 0.3 mA.

Table 2. Contraction patterns of extraneural stimulation followed by intraneural stimulation of the most superficial part of the brachial plexus

			Intraneural stimulation					
		(n)	elbow flexion	elbow extension	pectoral contraction	deltoid contraction	wrist flexion	wrist extension
Extraneural stimulation	elbow flexion	11	11					
	elbow extension	11		6		1		4
	pectoral contraction	5	2		1	2		
	deltoid contraction	3		1	1	1		
	wrist flexion	3	2	1			-	
	wrist extension	6	1	3			2	-

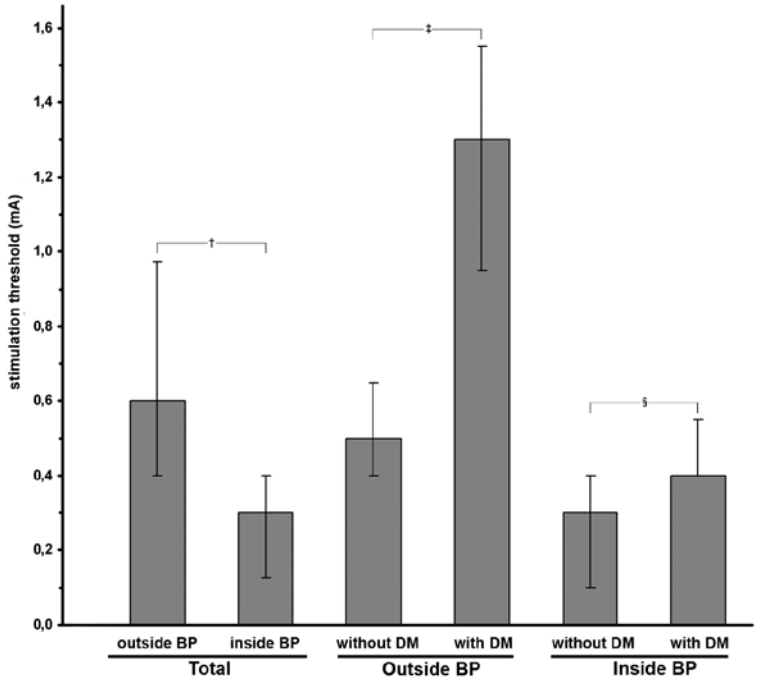


Figure 2. Bars displaying the median and interquartile range (IQR; 25 - 75%) of minimum stimulation thresholds (mA) outside and inside the brachial plexus measured from the most superficial part of the brachial plexus (BP) in all patients (total), diabetic patients (with DM), and non-diabetic patients (without DM). DM: diabetes mellitus. †: $p < .0001$; ‡: $p < .0001$; §: $p < .005$.

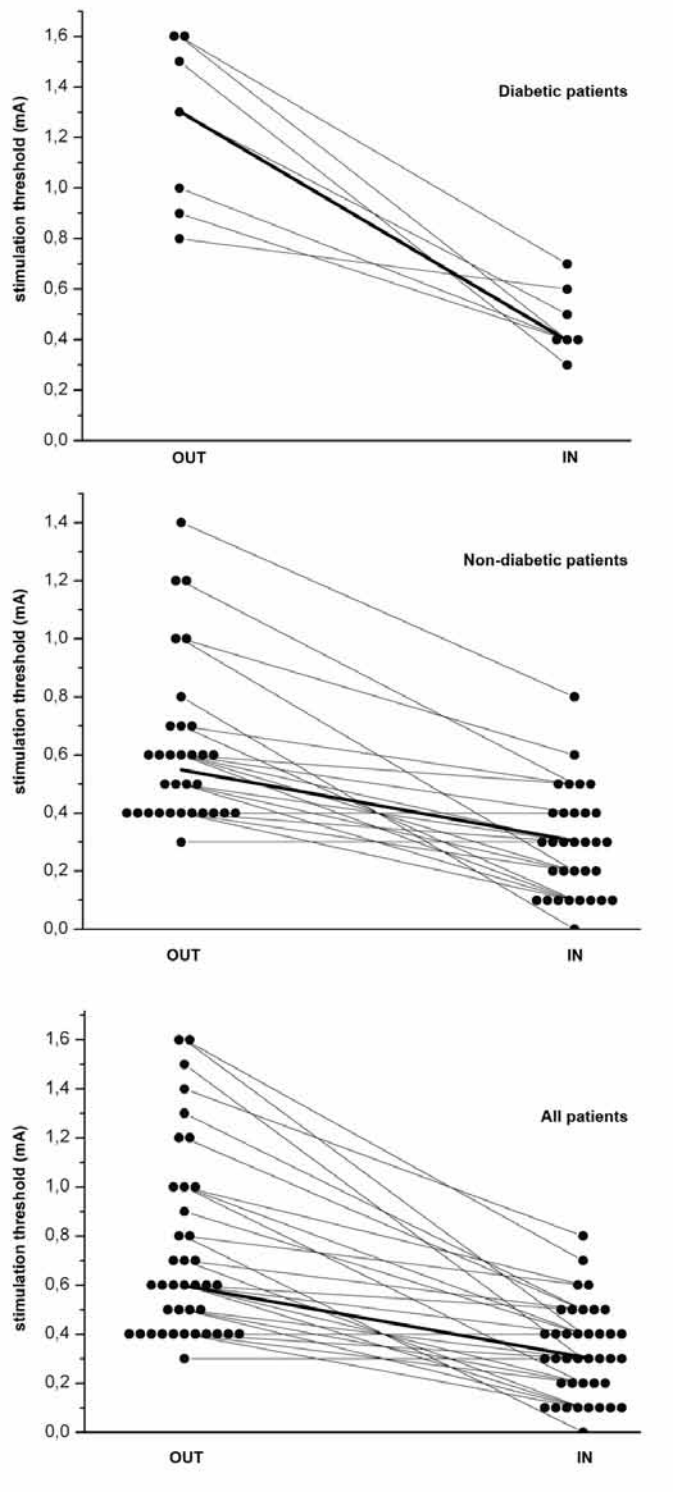


Figure 3. Minimum stimulation thresholds (mA) outside and inside the nerve in diabetic, non-diabetic and all patients. Bold lines represent the median.

The difference between the minimal stimulation current outside and inside was statistically significant ($p < 0.0001$).

All patients had akinetic, insensate limbs (motor = 0, sensory = 0) in all four nerve distributions at 20 min after blockade. In two patients, the anesthesiologist experienced high resistance to injection within the trunk. Both of these patients experienced pain during attempted injection. In these patients, the needle was withdrawn from the trunk and a total of 10 ml of local anesthetic was infiltrated around the trunk without pain. In all other included patients, injection proceeded easily without pain.

Diabetes mellitus

Of the included patients, seven were prediagnosed with diabetes mellitus, of whom two were insulin-dependent. The remaining five patients took combinations of sulfonylureas (glipizide, glyburide glimepride), bigaunides (metformin), or thiazolidinediones (rosiglitazone, troglitazone). Polyneuropathy related to the eye (fundoscopic examination) or foot (pinprick, brush, vibration, proprioception) was diagnosed in three patients, but none had any sensory or motor dysfunction in the upper extremities. The median (IQR) duration of the disease after diagnosis was 12 years (5, 33). On admission, the median (IQR) fasting blood glucose and hemoglobin A1c levels were 8.1 mmol/l (4.6, 11.5) and 6.8% (6.7, 8.1) respectively. Overall, higher stimulation thresholds were needed outside ($p < 0.0001$) and inside the nerve ($p < 0.005$) compared to nondiabetic patients (Figure 2). In two patients, the difference of stimulation threshold between outside and inside was 1.2 mA. In 86% of diabetic patients, a difference equal to or greater than 0.5 mA was observed compared to 30% in nondiabetic patients.

Contraction pattern

The contraction patterns associated with stimulation of the brachial plexus are presented in table 2. In 49% of patients (19 of 39), a similar contraction was seen outside and inside the trunk. In 74% (29 of 39) a typical pattern attributed to the superior trunk was observed, compared to 26% (10 of 39) attributed to the middle or inferior trunk.

Follow-up

Three patients reported localized pain without radiation at the injection site at 48 hours, which resolved gradually and spontaneously at three weeks without additional medication. None of them had any measurable sensory or motor defects postoperatively. Two patients reported numbness at 48 hours. One of them who had an open reduction and internal fixation of his fifth metacarpal bone reported numbness in the fifth finger on the side of the surgical incision, which resolved at 5 weeks. This patient exhibited elbow flexion during extraneural and intraneural stimulation of his block. The other patient who had a palmar fasciectomy for a Dupuytren's contracture reported numbness in the palm of his hand, which resolved at 3 weeks. This patient exhibited elbow extension during extraneural stimulation and wrist extension during intraneural stimulation. Neither patient showed any sign of motor deficit. Both of the patients who had pain on attempted injection had normal exams at 72 hours, 3 weeks and 6 months. Thirty-four patients had normal sensory and motor examination at 6 months follow-up. The remaining five patients were lost to follow-up.

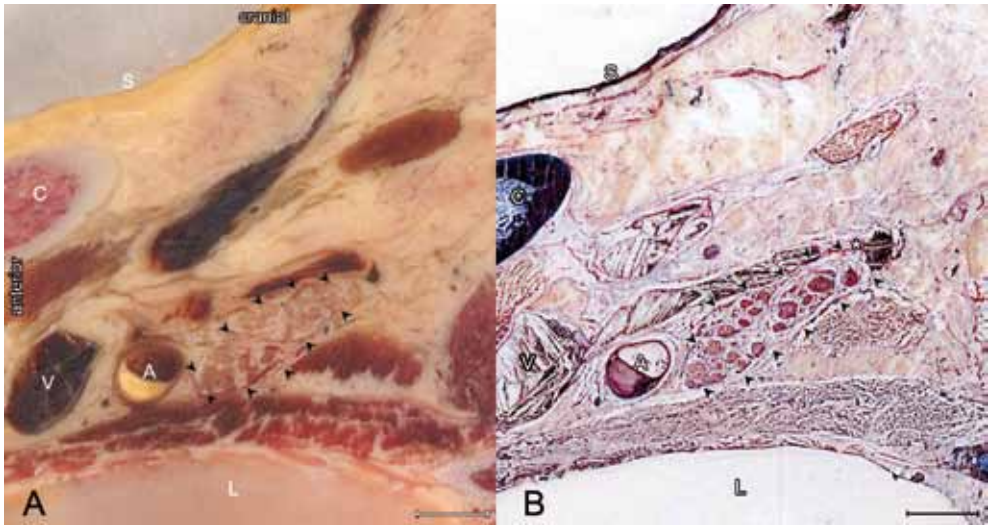


Figure 4. **A.** A cross-sectional overview of the anatomy of the brachial plexus in the supraclavicular region (sagittal plane) from a 63 years old female cadaver with end-stage kidney disease (Body Mass index 25.9 kg/cm^2) **B.** Histological overview of the same plane. *A,V, subclavian artery and vein; c, clavicula; S, skin surface; L, lung; arrowheads* indicate the epineurium, which refers to the outer border of the brachial plexus. *Asterisk* (*) *indicates the most superior part of the brachial plexus.* Note that identification of individual trunks is visually difficult. *Scale bar* = 10 mm.

Discussion

The present study is the first study comparing intraneural versus extraneural stimulation thresholds in humans. In 54% of patients, intraneural stimulation thresholds between 0.2 and 0.5 mA were observed. This is an interesting observation since many practitioners of regional anesthesia believe that the current level recommended for accurate current delivery while minimizing nerve injury or patient discomfort falls within this same range.[14,24-26] A comparative study on pigs reported a 21% incidence of intraneural stimulation with muscle contraction when the minimum current ranged between 0.2 and 0.5 mA.[16] This lower percentage compared to 54% found in our report may be explained by several factors such as physiologic differences between pig and human nervous tissue, dissected versus undisturbed anatomy, the number of subjects in each study, and differences in techniques. However, in both investigations, in a considerable percentage of subjects, intraneural needle placement could not be reliably differentiated from extraneural placement when a pulse duration of 0.1 *msec* and stimulation threshold greater than 0.2 and less than or equal to 0.5 mA was applied.

None of the stimulation thresholds outside the trunk were 0.2 mA or less. Thus, a contraction with a stimulation threshold of 0.2 mA or less with a pulse duration of 0.1 ms appears to be a reliable predictor of intraneural needle position in patients with normal sensory-motor examination. Recently in pigs, Tsai *et al.* found similar stimulation thresholds for intraneural position of the needle.[17] However, clinicians should not assume that the same results will be observed with different needles or stimulation generators or at other sites of the brachial plexus. The inconsistency of eliciting a motor response with electrical nerve stimulator has been shown by Urmey and Stanton.[27] A sensory response following

needle contact with a nerve may not always be accompanied by a motor response, which indicates some degree of insensitivity with the nerve stimulation technique.

In the subgroup of patients with diabetes mellitus, higher stimulation thresholds were needed outside as well as inside the trunk compared to patients without diabetes mellitus. This difference is statistically significant, but the small number of the diabetic patients included in this study necessitates caution if the findings are to be implemented in daily practice. Although higher stimulation thresholds to elicit motor responses in diabetic patients have also been reported in case reports,[28-30] its routine application remains to be elucidated in a larger group of patients. The underlying mechanism remains unclear, but involves a progressive impairment of sensory and motor function.[31] In addition, studies indicate that patients with diabetes mellitus experience progressive decreases in nerve conduction velocity and amplitude in sensory and motor nerves.[32]

An important limitation of the study is the exclusion of 29% of cases, which limits the interpretation of the findings to the general population. This may be attributed to both technical and patient-related factors. Technically, with ultrasound it is not always possible to reliably identify nerves. In a recent review, it was concluded that "…most ultrasound-guided clinical studies reported problems with obtaining satisfactory nerve images in some of their patients".[33] In a recent study, the supraclavicular brachial plexus was not adequately imaged in 21% of the patients.[34] With regard to the patient characteristics, the excluded patients were older and showed a significantly higher BMI than the included patients, challenging the reliability of ultrasound in detecting the exact location of the needle tip in these patients. This has also been reported for ultrasound guided interscalene block.[35]

Despite the methods we used to ascertain the location of the needle tip, two important findings may suggest that ultrasound may not always adequately determine the location of the needle tip as inside or outside the nerve. First, the fact that 23% of subjects (n = 9) required stimulating currents 0.5 mA or higher to acquire a motor response despite the needle tip being (presumably) inside the nerve may suggest an unreliable determination of needle location. Thus, it is possible that the observed differences in stimulation thresholds were caused by some uncertainty regarding the exact position of the needle tip. However, we consider this unlikely, since our findings are in keeping with earlier studies.[16,17,34] Second, the fact that 51% of stimulations did not demonstrate similar motor responses when stimulating outside versus inside the nerve, further suggests an unreliable (and variable) determination of needle tip location.

However, the different motor responses outside and inside the nerve may also be related to the anatomic configuration of the nerve. More than 50% of the brachial plexus in the supraclavicular region is composed of fat and connective tissue.[36] This implies that the local tissue environment 'outside' and 'inside' the nerve may differ substantially, and thus the electrical current conduction characteristics of the tissue. Moreover, the distribution of neural tissue 'inside' may further affect electrical current conduction. Connective tissue around the nerve may conduct the current in a different manner than the nonneural tissue inside the nerve. Furthermore, peripheral nerves are a heterogeneous mix of sensory and motor fascicles.[37] As the needle pierces the epineurium, the nerve often begins to rotate and compress.[20] The final position of the needle within the nerve may lie next to a different fascicle compared to the outside stimulation. Finally, no difference of stimulation current was observed between outside and inside the nerve in 13% of cases. The aforementioned

reasons for the poor correlation of the contraction patterns could also apply for this observation.

The validity of high-resolution ultrasound in positioning the needle at the desired location, *e.g.,* directly adjacent to a nerve or even inside the nerve, has been shown to be high, as reported in other regions.[19,38] Eichenberger *et al.* have shown that 33 of the thirty-seven needle tips were located at the exact target point.[38] Sauter *et al.* have successfully implemented high-frequency ultrasound in the study of stimulation thresholds and different distances to the nerve to obtain motor responses.[19] Needle tip visualization and indentation of the nerve wall were described as indicators for needle-to-nerve contact.[19] The question remains regarding which layer is being contacted and indented. One generally assumes that the most outer border of the nerve is constructed of epineurium. In both anatomical and histological examination of the trunks in the supraclavicular area, the epineurial layer is easily identified (Figure 4). It is arguable whether this layer represents a continuation of the prevertebral and anterior and middle scalene muscle fascia. However, by puncturing this immediate outer layer, an opening is created into the inner environment of the nerve or trunk. Inside the trunk, this space is filled with fat and connective tissue surrounding the perineurium, which accounts for 52% of the brachial plexus cross-sectional area.[36] The perineurium encapsulates bundles of nerve fibers and is referred to as the actual nervous tissue or nerve fascicles. On ultrasound, the nerve fascicles appear as distinct round- to oval-shaped hypoechoic nodules.[20,39] It was found technically feasible to place the needle tip adjacent to these nodules, thus assuming an intraneural position of the needle tip, although its validity needs to be confirmed in future investigations. In our study, we used the injection of small amounts of local anesthetic followed by the characteristic distension of the nerve, both described as indicators for intraneural injection,[16,21-23] as final verification. Only patients in whom all experts agreed upon extra and intraneural position of the needle included; therefore, we believe that our data is reliable in this respect.

In the included patients, measurements were done in the most superficial part the brachial plexus. It is tempting to say that this is actually the superior trunk. Recognizing the superior trunk in the supraclavicular region provides some difficulties due to the technical limitations,[40] individual variability,[41] and the close relationship between the trunks. This is best seen in figure 4 where the trunks have been formed in the supraclavicular region, but are difficult to demarcate individually. The observed contraction patterns demonstrate that, under ultrasound guidance, the most superficial part of the plexus is not always the superior trunk. In fact, a typical pattern attributed to the superior trunk was observed in only 74%. This indicates that the cords have already been formed in the cases where a middle trunk response-type was found. It may also indicate that the tip of the needle was advanced through the superior trunk into the confines of the middle trunk. Nonetheless, whether the stimulation threshold was measured from the superior or middle trunk, the observed differences remain reliable, since stimulation of either trunk occurred intraneurally.

Two patients reported numbness postoperatively, which would account for a short-term injury rate of 5%. The relation between both injuries and the technique of nerve block is arguable. For confirmation of the intraneurally placed needle tip, a small amount of up to 5 ml of local anesthetic was injected. This could increase the risk of (short-term) injury. If associated with the nerve block itself, this rate could be regarded as high. However, in one patient, the numbness in the fifth finger was closely related and demarcated by the surgical incision side which makes it unlikely that the origin of the numbness was related to the

technique of the nerve block. Furthermore, the second patient showed numbness of the palm after a palmar fasciectomy. The rate of nerve injury after fasciectomy in the surgical literature has been reported to be between 1.5% and 7.8%.[42,43] In light of the surgical site and the incidence of nerve injury in the surgeon's hands, it is likely that the numbness is related to the surgery rather than the nerve block. An additional argument favoring this assumption is the fact that both patients showed a muscular contraction after intraneural placement of the needle that was not in the same sensory distribution area of the numbness. This observation would reduce the probability of the nerve block to cause nerve injury.

Recent observations in ultrasound-guided axillary block with visually confirmed intraneural injection of the local anesthetic showed that this injection does not invariably cause neural injury.[21] However, this should not change clinical practice. The basic rule not to inject local anesthetics into the nerve remains. The limit of 0.2 mA should therefore be regarded as a safety level to detect intraneural needle position in electrostimulation-guided blocks of the brachial plexus. Further studies investigating the relation between intraneural injection and the development of neurologic damage are required.

In summary, clinically relevant differences in stimulation thresholds have been shown between outside and inside the nerve. Yet, these differences have to be interpreted in light of the possible inaccuracy of ultrasound to detect the exact location of the needle tip. Taking into account that the ultrasound was able to clearly detect the location of the needle tip in only 69% of cases, we consider stimulation currents of less than or equal to 0.2 mA reliable to detect intraneural position of the needle. Furthermore, stimulation thresholds greater than 0.2 and less than or equal to 0.5 mA could not rule out intraneural placement of the needle. Diabetic patients require higher stimulation thresholds both outside and inside the nerve to elicit a motor response.

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Addendum

Ultrasound-guided supraclavicular block may be intraneural

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To the editor:

We thank Drs. Morfey and Brull for their response to our recent observations.[1] They raise some important questions on the ability of minimum stimulating current to detect intraneural needle placement and to predict neurologic injury after intraneural injection. Their most important question, however, concerned the reliability of our measurements: How sure are we that the needle tip was outside and inside the nerve during extraneural and intraneural measurements, respectively? Their question concerning what would be the outer layer of the supraclavicular brachial plexus is very reasonable. In their ultrasound-guided supraclavicular block procedure, accompanied by figures prior to and after injection, they describe that during the block this outer layer is intentionally breached, which is often felt as a loss of resistance or 'pop'.

We have the same experience. At this site the nerve fascicles are surrounded by epineurial layers, as shown in our figure 4 of our article.[1] The configuration of epineurial layers may differ depending upon the site of formation of the nerve trunks and cords of the brachial plexus. In addition, as stated in our discussion, adjacent to the epineurial layers, fascial layers that are continuous with the prevertebral and scalenic muscle fascias may be present. This can be better observed in an axial histological cross-section (Figure 1) that evidently shows several layers surrounding the nerve fascicles, including an outer layer, that cannot always be clearly separated from the adjacent epineurial layers. Both layers are very thin ($\leq$ 0.2 mm). Thus, by intentionally breaching this layer, we believe that both layers are punctured, and the needle tip is inside the nerve, which we referred to as intra-epineurial.

However, to objectively verify this position we adopted two additional parameters, *i.e.* the position of the needle tip adjacent to the hypoechoic (black) round to oval-shaped nodules combined with distention of the nervous structure after small volume injection. For that reason, it might have been more appropriate to define 'inside the nerve' as parafascicular (next to the nerve fascicles). The outside location was verified by indentation of a hyperechoic layer by pressure from the needle tip and by the absence of nearby black nodules. This could have been described as non-parafascicular. Thus, we are confident that our measurements really represent intraneural and extraneural needle tip placement. In fact, the accompanying figures of Morfey and Brull show the same configuration of black, round to oval-shaped nodules. Unfortunately the position of their needle during injection is not shown. Furthermore, they suggest that if they accept our description and conclusions, they may have performed intraneural injections of the supraclavicular fossa much of the time. Actually, their figure 2 can be considered as a confirming sign that shows what has actually happened during their blocks, but what always was difficult to interpret: The presence of local anesthetic fluid adjacent to nerve fascicles. Since their retrospective survey did not reveal long term neurologic injury,[2] it underlines our previous statement that intraneural injection does not invariably result in neurologic injury.[3,4]

The relative amount of connective tissue in combination with the thinness of epineurial and outer layers may further explain this phenomenon.[4] Our findings may be generalisable

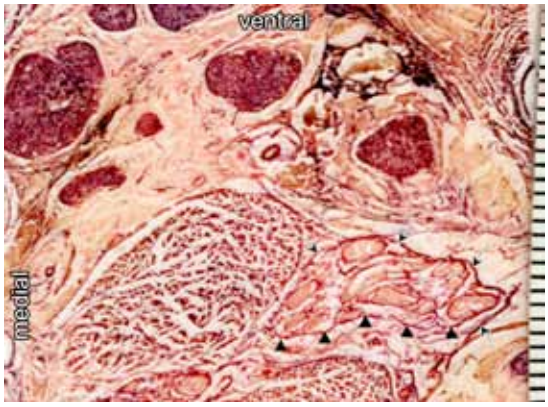

Figure 1. Axial, histological, cross-section of the brachial plexus near the supraclavicular region. Note the two distinct layers around the nerve fascicles: prevertebral and scalenic fascia (arrows) and epineurium (arrowheads). Mallory-Cason trichrome staining.

to nerves at other anatomic sites. Recently, Robards *et al.* reported findings that are similar to ours for the popliteal sciatic nerve block.[5] They observed intraneural injection in all cases with a motor response at a stimulation current 0.2 - 0.4 mA. So, our conclusion that stimulation thresholds >0.2 mA and ≤0.5 mA are not reliable to prevent intraneural needle tip position was verified at a second anatomical site.

In conclusion, a minimum stimulation threshold of ≤0.2 mA is reliable for parafascicular placement of the needle in ultrasound-guided supraclavicular block, and possibly for other anatomical sites as well. Can this minimum current predict whether needle placement and local anesthetic injection will cause neurological injury? No, it can not. Are we convinced that our measurements inside and outside the nerve are reliable? Yes, we are convinced. Finally, are the ultrasound-guided supraclavicular blocks of Drs. Mofrey and Brull actually intraneural? Yes, that is our opinion, when anesthetic fluid is found adjacent to nerve fascicles.

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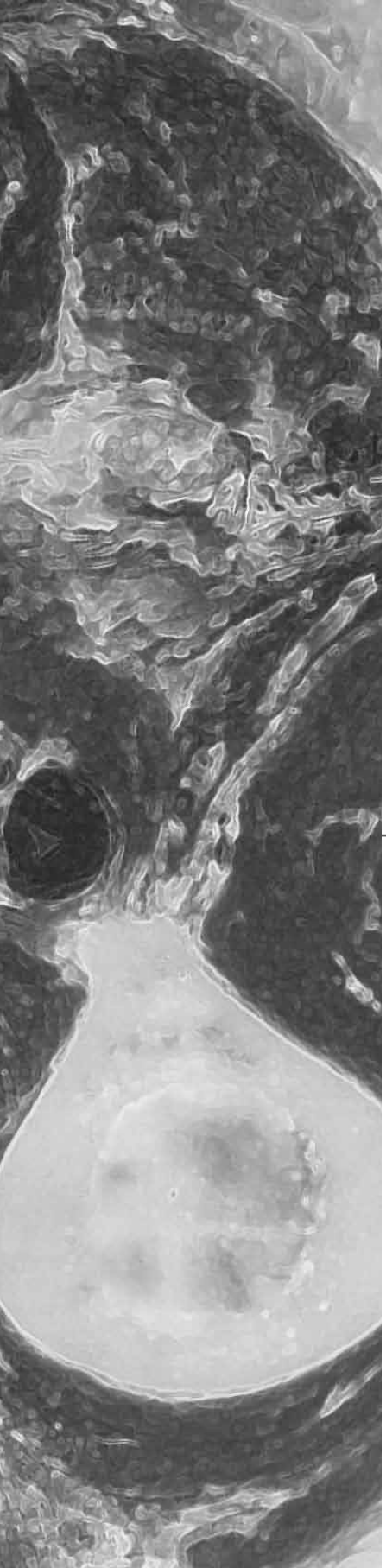

Chapter 10

Diagnostic Accuracy of Ultrasound Parameters to Detect Small Volume Intraneural Injection in Regional Anesthesia

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Submitted

Abstract

Background **Intraneural injection is considered a major risk factor for neurological sequelae. To minimize this risk, ultrasound might be helpful. Various parameters for ultrasonographic detection of intraneural injection have been described, all with large volumes (5 - 40 ml). The aim of the present study is to determine the diagnostic accuracy of ultrasound parameters to early detect intraneural injection in supraclavicular brachial plexus and infragluteal sciatic nerve block.**

Methods **Using ultrasound, in 9 consecutive unembalmed human cadavers, the bilateral supraclavicular brachial plexus and infragluteal sciatic nerve were injected intraneurally with 0.5 ml of 1% methylene blue. Predefined criteria for intraneural injection were: 1) indentation of nerve wall, 2) visualization of needle tip adjacent to nerve fascicles, and 3) distension of nerve diameter combined with change in echogenicity. The supraclavicular and infragluteal regions were removed en bloc. Using cryomicrotomy as gold standard, consecutive anatomic and histologic cross-sections (interval 50 μm) were obtained. Two independent experts assessed intraneural presence of the injectate and the ultrasonographic recordings.**

Results **A total of 36 injections were performed, of which 33 (92%) intraneurally. Increase in nerve surface area with change in echogenicity was the single most sensitive parameter to detect intraneural injection (positive predictive value, PPV: 94% [95% CI, 87 - 100]). For supraclavicular brachial plexus, indentation of the nerve wall and visualization of the needle tip next to nerve fascicles were less predictive for intraneural injection (PPV: 88% [95% CI, 71 - 100], 83% [95% CI, 62 - 100], respectively).**

Conclusion **In this anatomic study, small volume (0.5 ml) intraneural injection was reliably detected with ultrasound. The most accurate ultrasonographic parameter for intraneural injection was expansion of nerve diameter combined with change in internal echogenicity.**

Nerve damage is a rare but feared complication in the practice of regional anesthesia. One of the presumed etiologic factors is believed to be intraneural injection.[1] Recent findings in animal and human studies suggest that application of conventional techniques such as nerve stimulators do not prevent intraneural injection.[2-4] Since stimulation thresholds between 0.3 – 0.5 mA, generally regarded as safe, do not distinguish between intra- and extraneural needle tip location, ultrasound should be applied to detect an intraneural position.[2] Its use has been postulated to decrease the risk of injection inside the nerve.[5] However, even with ultrasound guidance, intraneural injection has been repeatedly reported.[6-8] Although recent literature has shown that intraneural injection does not invariably cause neurological damage,[9,10] experts still believe that intraneural injection should be avoided to minimize neurological sequelae.[1]

Ultrasound has been utilized for intraneural injection on macroscopically exposed nerves.[3] It is generally accepted as an accurate tool to deliver the local anesthetic at the desired location.[11,12] In clinical practice, however, nervous structures are surrounded by fascia, muscles, bony structures and adipose and connective tissue, which interfere with the ability of visualizing the exact position of the needle tip inside or outside the nerve. Furthermore, adequate visualization of nervous structures is not always possible in all patients.[13] A number of (in)direct visual parameters to detect intraneural injection have been proposed, which could be of help to distinguish between intraneural and extraneural injection. They include visual tracking of the needle tip penetrating the nerve after indentation of the nerve wall,[14] change in echogenicity and expansion of the nerve structure, and visualization of the needle tip next to nerve fascicles.[2,4,8,9,15] These characteristics are relevant indicators for intraneural injection, but their separate accuracy has not been investigated yet, especially since they were applied in studies in which relatively large volumes of local anesthetics were used (5 – 40 ml).[2,4,9] However, even very small amounts of local anesthetic in the range of 0.5 ml have been suggested to cause injury to nerve fascicles.[16-18] Therefore, early identification of small volume intraneural injection is vital.

The lack of a reliable gold standard to objectively compare ultrasound with, is a major drawback. Conventional imaging modalities such as computer tomography or magnetic resonance imaging are not an option for it is practically impossible to use these modalities in real-time during the procedure. In addition, their resolution is limited. A high-resolution gold standard is needed, which reliably differentiates between intraneural and extraneural compartments, and in which the anatomy of the nervous tissue after intraneural injection remains unaltered. Cryomicrotomy is considered the present gold standard for undisturbed, high-resolution anatomy.[19-21]

We hypothesize that high-resolution ultrasound reliably detects small volume intraneural (intra-epineural) injections. To test our hypothesis, we determined the diagnostic accuracy of ultrasound by calculating the positive predictive value of the available ultrasound parameters after ultrasound-guided, intraneural injection of dye in the brachial plexus and sciatic nerve of unembalmed, fresh cadavers. We used cross-sectional and histologic slices obtained by cryomicrotomy as gold standard to confirm the presence or absence of intraneural injection.

Materials and methods

Nine consecutive cadavers were selected within the donor program of the Department

of Anatomy of the University Medical Center Utrecht, Utrecht, The Netherlands, after institutional review board approval from the same department. Exclusion criteria were knowledge of existing brachial plexus or sciatic nerve pathology. All cadavers were injected within 12 hours post-mortem.

Definitions

Penetration of the most outer epineurial layer of the nerve is mandatory for intraneural placement of the needle tip. Inside, the nerve contains nerve fascicles surrounded by perineurium and an intra-epineurial stroma of connective tissue surrounding the fascicles. On ultrasound, the surrounding stroma appears as relative hyperechoic (white), whereas the nerve fascicles show as hypoechoic (black) spots.[5]

Dye selection

A pilot study was done to determine the potential diffusion capacity of the dye into the nerve after extraneural placement of the dye. Methylene blue has been previously used for accuracy and positioning studies of nerves.[22,23] Therefore, we chose a volume of 0.5 ml of methylene blue 1% for detection of intraneural injection. A total of 0.5 ml was injected directly on the surface of an exposed, unembalmed, supraclavicular brachial plexus at two separate locations (site A and B). After harvesting the sites, using a cryomicrotome, cross-sections with an interval of 0.5 mm were obtained from site A, and directly examined under the microscope to determine the extent of diffusion of the dye. Site B was immediately embalmed in a solution of 3.5% formaldehyde and frozen to minus 30°C. After 24 hours, histologic and cryosections with an interval of 0.5 mm were obtained for microscopic examination.

At side A, the dye was found in the epineural, as well as perineural area, whereas at site B the dye was only observed in the outer epineural layer. Therefore, we choose the procedure described for site B for all subsequent cadavers.

Ultrasound

In the supine position, both supraclavicular regions of each cadaver were scanned with an 10-18 MHz linear array transducer (MyLab30CV, Esaote, Maastricht, the Netherlands). The probe was positioned in the supraclavicular fossa according to the modified Plumb-Bob approach, in an oblique sagittal orientation and perpendicular to the axis of the brachial plexus.[24] Under real-time ultrasound guidance, a 22-gauge, 50-mm, short bevel needle (Pajunk GmbH, Geisingen, Germany) was inserted parallel to the long axis of the transducer in the supraclavicular fossa. The brachial plexus appeared as distinct round- to oval-shaped hypoechoic nodules embedded in a hyperechoic area, and encircled by a hyperechoic line. The most superficially visible trunk of the brachial plexus was targeted. A total of 0.5 ml of methylene blue 1% was injected during 5 seconds.

For the infragluteal regions, an 7-13 MHz linear array transducer was used in both legs in the prone position. The transducer was placed caudal to the subgluteal fold, perpendicular to the axis of the sciatic nerve. In this region, the sciatic nerve appeared as a triangular to round structure with hypoechoic spots, and hyperechoic areas. For the sciatic nerve, a 22-gauge, 100-mm needle was used. Again, a total of 0.5 ml of methylene blue 1% was injected during 5 seconds.

To assess the consistency of ultrasound, three individual parameters suggestive for intraneural injection were defined (Figure 1). These include:

1. visualization of the needle tip during penetration of the nerve or inside the nerve adjacent to the hypoechoic (dark) spots,[2]
2. indentation of the nerve wall (*i.e.*, hyperechoic outer layer),[2,14]
3. visible expansion of the cross-sectional area of the nerve in combination with change in echogenicity.[3,4]

All parameters were assessed as dichotomous values. Ultrasonographic visibility of the needle tip during penetration or injection was noted as follows: (-) not visible, and (+) clearly visible; indentation of the nerve wall was noted as follows: (-) no indentation visible; and (+) clear indentation visible, after which the wall sprang back following further advancement of the needle (pop effect); expansion of cross-sectional surface area of the nerve was assessed as follows: (-) no visible change in diameter or echogenicity of the nerve; and (+) visibly clear increase in the cross-sectional area in combination with change in echogenicity owing to an increase of hyperechoic areas within the nerve. We did not set a cut-off level for the increase of nerve surface area, because some of the putative intraneural injection attempts would be excluded. The relative increase in nerve surface area was independently determined by two investigators immediately after the block and the average of two measurements was used for final analysis. Ultrasound-guided intraneural injection was presumed if a positive score was given for one or more of the three parameters.

After the injection procedure, the cadaver was immediately embalmed and frozen as described earlier for site B. The scanning procedures and injections were all performed by one investigator with experience in ultrasound-guided regional anesthesia (N.M). All parameters were assessed separately by two physicians with expertise in ultrasound-guided regional anesthesia.

In addition to the ultrasonographic assessment, pressure was also monitored during injection. A calibrated manometer (BSmart, Concert Med. LLC, Norwell, MA) was attached between the syringe and the needle. The manometer provided a coloured, interval scale of the pressure throughout the injection (white, 1-15 psi; yellow, 15-20 psi; orange, > 20 psi).

Cryomicrotomy and histology

To minimize spread of the dye by manipulation of the nerves or surrounding tissues during dissection, the anatomy was left undisturbed. The complete area between the lateral side of the interscalene region and the midclavicular area was removed en bloc. For the lower extremity, the same was done for the upper leg 3 cm proximal and 3 cm distal to the injection site. The specimens were then frozen in carboxymethylcellulose gel at minus 30°C. Using a heavy-duty sledge cryomicrotome (PMV 450; LKB Instruments, Stockholm, Sweden), consecutive sagittal (supraclavicular region) or transversal (upper leg) sections (interval, 50 μm) 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. An independent investigator, blinded for the injections, assessed the images to confirm or reject the presence of methylene blue staining within the confines of the epineurium of the nerves. Histologic sections with an interval of 5 mm were stained using a modified Mallory-Cason procedure.[25]

Statistical analysis

Data are presented as means ± SD and percentages with 95% confidence intervals (95% CI). Cadavers were consecutively selected between June 2008 and June 2009, with approximately one cadaver per month due to the elaborate and time-consuming technique of cryomicrotomy. Finally, we collected a total of 9 cadavers plus one cadaver for the pilot. Assessment of the ultrasound criteria was done by calculating the positive and negative predictive value (PPV, NPV) for each of the parameters for intraneural injection. Based on earlier findings for large volumes,[2] we expected to find a PPV between 70 and 95%. With 36 attempts of ultrasound-guided intraneural injection, it is possible to detect a value for PPV (95%CI) between 0.7 (0.57-0.83) and 0.95 (0.89-1.0), according to worst and best case scenario. Loglinear analysis was used for the added value of individual ultrasound-related characteristics to detect intraneural injection. For comparison of proportions and means, the dependent $\chi 2$ and students t-test were respectively used. P-values less than 0.05 were considered significant. Statistical analysis was performed using SPSS Statistics version 17.0 (SPSS Inc., Chicago, IL).

Results

All nine cadavers (8 female and 1 male) were included for final analysis. The average age and body mass index were 86.4 ± 6.8 yr (range, 73 – 95 yr) and 21.6 ± 5.1 kg/m^2 (range, 13.3 – 28.7 kg/m2), respectively. A total number of 36 attempts of intraneural injections were performed, distributed equally over the supraclavicular brachial plexus and infragluteal sciatic nerve. In all attempts, intraneural injection was independently concluded by all experts based on the positive score of one or more of the predefined criteria for ultrasound-guided intraneural injection (Figure 2). The anatomic and histologic cross-sections revealed intraneural presence of the injectate in 33 out of 36 cases (92%). There was no evidence of intraneural presence of dye in two attempts at the supraclavicular brachial plexus and one at the infragluteal sciatic nerve.

Table 1 shows the absolute and relative values of nerve surface area for brachial plexus, sciatic nerve and overall, before and after injection. This is based on the 33 confirmed attempts of intraneural injection. Overall, injection of 0.5 ml of injectate resulted in a relative increase of nerve surface area of 8.7% (95%CI, 5.6 – 11.9). The highest relative increase in nerve surface area was seen in the sciatic nerve, *i.e.*, 9.4% (95%CI, 4.6 – 14.2%), whereas for the brachial plexus, an increase was observed of 8.0% (95%CI, 3.4 – 12.6%).

Table 1. Absolute and relative increase in nerve surface before and after injection of 0.5 ml of injectate

	Nerve surface area				
	before injection*	after injection*	abs. difference**	rel. difference (%, 95%CI)	p
BP	52.2 ± 12.2	56.2 ± 12.9	4.0 (1.7 – 6.4)	8.0 (3.4 – 12.6)	< 0.001
SN	64.2 ± 14.1	70.1 ± 16.0	5.8 (3.0 – 8.7)	9.4 (4.6 – 14.2)	< 0.001
Overall	58.2 ± 14.5	63.1 ± 16.1	4.9 (3.2, 6.7)	8.7 (5.6 – 11.9)	< 0.0001

Values are presented as *) mm2 mean ± SD, or (**) mm2 mean (95%CI).
† Dependent, one-sided, Student's t-test for the difference before and after injection.

Table 2. Identification of individual ultrasound characteristics

			Ultrasound characteristics					
	Intraneural?†		Parameter 1		Parameter 2		Parameter 3	
	N (%)		+	-	+	-	+	-
BP	16/18 (89)	+	10	6	14	2	16	0
		-	2	0	2	0	1	1
			83 (62–100)*	0**	88 (71–100)*	0*	94 (83–100)*	100**
SN	17/18 (94)	+	15	2	16	1	17	0
		-	1	0	1	0	1	0
			94 (82–100)*	0**	94 (83–100)*	0**	94 (87–100)*	0**
Overall	33/36 (92)	+	25	8	30	3	33	0
		-	3	0	3	0	2	1
			89 (78–100)*	0**	91 (81–100)*	0**	94 (87–100)*	100**

Table showing the percentage of cases, per parameter and per location with the corresponding positive and negative predictive value. Each positive parameter was confirmed by cryomicrotomy and histology.
† Anatomic and histologic confirmation of presence of dye intraneurally. BP, brachial plexus. SN, sciatic nerve.
* Positive predictive value (% [95%CI]). ** Negative predictive value (% [95%CI]).
Parameter 1: visualization of needle tip adjacent to nervous tissue (fascicles); Parameter 2: indentation of nerve wall followed by puncture; Parameter 3: increase in nerve surface area in combination with change in echogenicity.

Table 2 presents the frequency of identification of each individual parameter with the positive and negative predictive values. All values are given as percentages (95%CI). Needle tip was visualized inside the nerve in 28/36 (78%) of cases, of which 25 correct (69%). Overall, the visualization of the needle tip was associated with a PPV of 89% (78 – 100) confirmed with cryomicrotomy and histology as gold standard. Separate assessment for the brachial plexus and sciatic nerve intraneural injection attempts showed a PPV of 83% (62 – 100) and 94% (82 – 100), respectively.

Clear indentation followed by puncture of the nerve wall was observed in 33/36 (92%) of cases, of which 30 correct (83%). Overall, indentation followed by puncture of the nerve wall was associated with a PPV of 91% (81 – 100). The fact that indentation followed by the puncture of the nerve was not seen in 3 cases, did not exclude intraneural injection. The individual PPV for the brachial plexus and sciatic nerve intraneural injection attempts was 88% (71 – 100) and 94% (83 – 100).

Expansion of the nerve area in combination with change in echogenicity was observed in 35 out of 36 cases (97%), of which 33 correct (92%). This is associated with a PPV of 94% (83 – 100) for either brachial plexus or sciatic nerve. In only one attempt, no change in diameter and echogenicity was observed. In this case, histologic examination confirmed absence of injectate inside the nerve, accounting for a maximum NPV of 100%. Compared with other ultrasound parameters, increase of nerve surface area combined with change in echogenicity is most strongly associated with intraneural injection ($p < 0.021$).

With the calibrated manometer attached between the syringe and the needle, it was not possible to determine the exact level of pressure. However, the pressure remained in the white range (between 0 and 15 psi) during all intraneural injections.

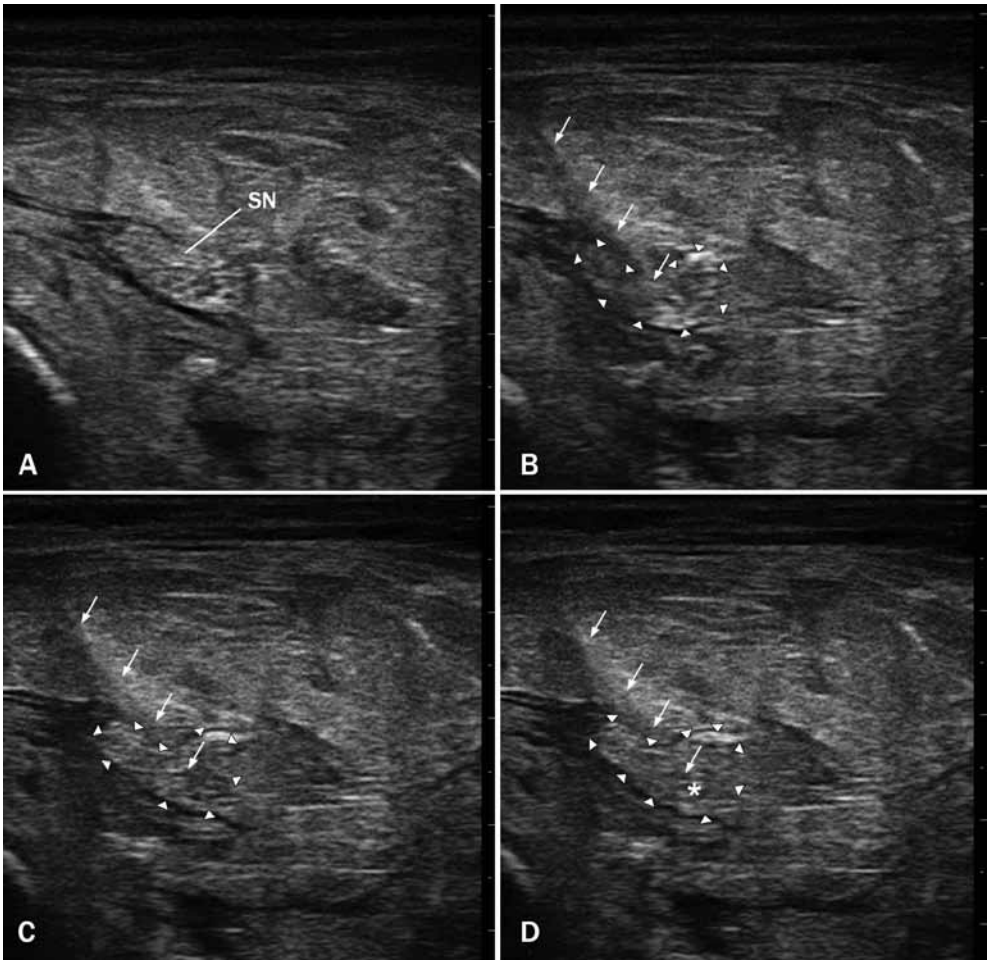

Figure 1. Ultrasound overview of the sciatic nerve, SN (A), insertion of needle and indentation of the nerve wall (B), needle tip inside the nerve adjacent to the nerve fascicles (C), and increase in nerve surface area in combination with change in echogenicity after injection of 0.5 ml of injectate (D). Arrowheads show the surroundings of the sciatic nerve, arrows point to the needle track. Asterisk shows immediate change in internal echogenicity.

Discussion

The current report is the first study validating in real-time intraneural injection parameters of ultrasound-guided blocks of supraclavicular brachial plexus and infragluteal sciatic nerve. This was achieved with a volume of as low as 0.5 ml. Increase in nerve surface area in combination with change in echogenicity was the single most accurate characteristic for intraneural injection. With this parameter, early identification of intraneural injection was possible in 33 out of 36 cases (92%).

Increase in nerve surface area has frequently been used as a separate indicator for intraneural injection.[2-4,6,9] In some cases, it is accompanied by the appearance of a hypoechoic ring around the nerve, referred to as a halo ring.[4,9] In our report, we used both increase of

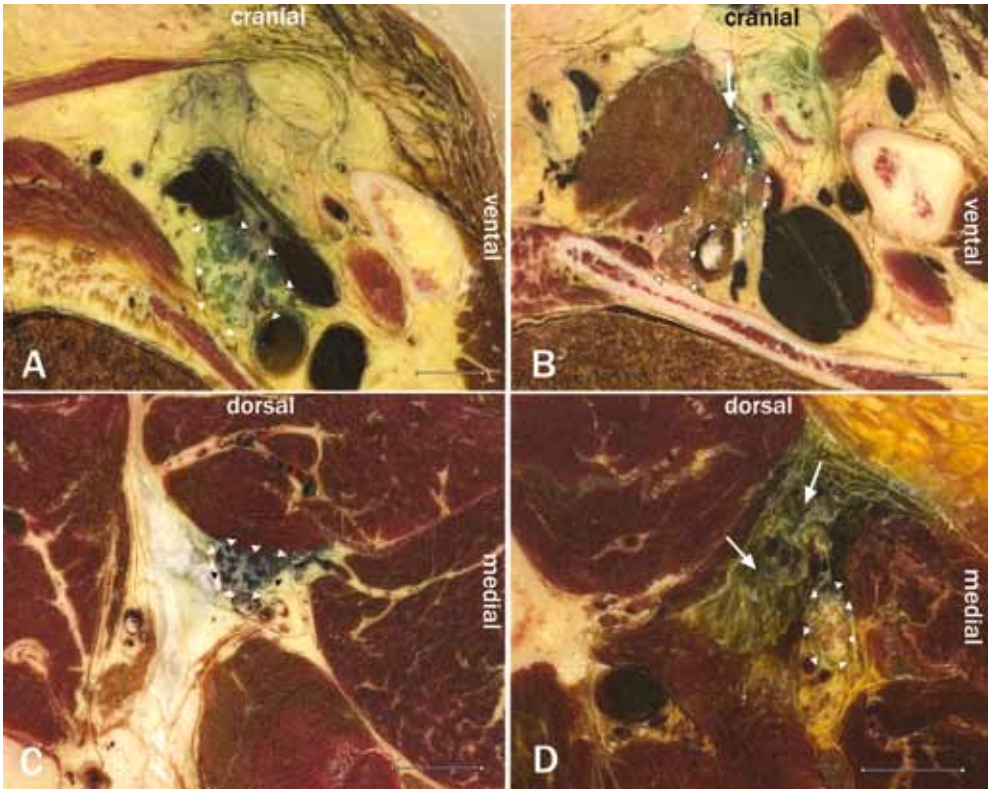

Figure 2. Cryomicrotome cross-sections showing the results of ultrasound-guided intraneural injection in the supraclavicular brachial plexus (A, dye inside; B, dye outside; arrow) and in the sciatic nerve (C, dye inside; D, dye outside; arrow). Bar = 1 cm. Arrowheads show the configuration of both nervous structures.

nerve surface area and change in echogenicity, since intraneural fluid immediately affects the ultrasonographic characteristics of a nerve.[26] The level of increase of the nerve surface area is highly related to the amount of local anesthetic and the type of nerve. In a recent report, an increase of 15% in nerve surface area was suggested as a reliable indicator for intraneural injection.[4] However, this was achieved by injection of 40 ml of local anesthetic, which seems a very large amount compared to the relative small increase of 15% or more in nerve surface area. It is unknown what minimum amount of local anesthetic would cause the nerve area to increase 15% or more. In our report we found an increase of 8% and 9.4% for the surface area of, respectively, the brachial plexus and the sciatic nerve, after injection of 0.5 ml of dye. This suggests that practitioners can be alerted for intraneural injection even after injection of very small amounts of local anesthetic.

Although not significant, ultrasonographic parameters for intraneural injection seem to be more consistent for the sciatic nerve compared to the brachial plexus. We believe that this could be related to the internal architecture and spatial configuration of the nerves. In the supraclavicular region, the trunks do not run parallel to one another and exchange nerve fibers for the formation of the cords. This irregularity in shape and trajectory causes the ultrasound beam to reflect in various directions and hence produce partly blurred images.

Furthermore, probe handling is hampered by the irregular surface of the supraclavicular region, which makes a perfect alignment of the needle under the probe difficult.[27] This is underlined in a recent review of ultrasound-guided peripheral nerve blocks.[13] The sciatic nerve on the other hand, usually follows a perpendicular straight down trajectory, which is easy to visualize and relatively superficial in the infragluteal region.[28,29] Nerve characteristics are therefore easily identified. In addition, other ultrasound parameters used in our study include visualization of the needle tip adjacent to the nervous tissue and indentation of the nerve wall followed by puncture. These two parameters show a slightly lower accuracy in detecting intraneural injection in the supraclavicular brachial plexus, compared to increase in nerve surface area with change in echogenicity. However, for the sciatic nerve, the accuracy of all three characteristics are comparable (94%). The aforementioned anatomic differences between nerve fibers and structure of brachial plexus and sciatic nerve could also explain the differences in accuracy.

In both animal and human studies, recent evidence suggests that intraneural injection does not inevitably cause neurological dysfunction.[2,4,9,10] Some hypotheses could be formulated for this observation. First, the internal architecture of the nerve may prevent direct damage. This is related to the amount of neural to nonneural tissue inside the nerve in the various parts of the nerves. For example, as much as 65% of the nerve in the distal region of the brachial plexus (shoulder) is composed of nonneural tissue.[20] This relatively high amount of nonneural tissue may provide a protective barrier against mechanical injury caused by the needle. Second, the perineurium is, in contrast to the epineurium, a mechanically tough and resistant layer.[30] It is unlikely that a blunt needle will penetrate it easily. In a recent study on human popliteal sciatic nerve, intraneural needle insertion was found more frequently interfascicular than intrafascicular.[31] In addition, in only 3.2% of cases, evidence of fascicular damage was reported. Thus, an intraneurally inserted needle is more likely to displace the fascicles and pass through the connective and adipose tissue without rupturing the perineurium. Third, the injected local anesthetic could escape from the nerve through the punctured area or by rupture of the epineurium caused by elevated intraneural pressure. This would theoretically lead to a decrease in pressure, and thus lowering the potential risk of nerve injury.[16]

Earlier studies have also addressed the diagnostic accuracy of ultrasound, however, they did not distinguish between intraneural or extraneural position of the needle tip. Eichenberger *et al.* reported an accuracy of 95% (95%CI, 84 – 98%) of successful needle localization for the inguinal nerves.[22] Similar success rates have been reported for the lateral femoral cutaneous nerve and the phrenic nerve.[32,33] Furthermore, in these studies, dissection was used as gold standard to verify the location of the needle tip. Cryomicrotomy for intraneural injection was not applied. The use of dissection in this respect seems to be controversial as it may disturb the local topography and spread of the injected dye, and as a consequence, displace the exact location of the injectate and surrounding structures. Additional imaging modalities have been used to accurately determine the exact location of the needle tip and nearby structures. Modalities such as computer tomography and magnetic resonance imaging have been utilized for validation of ultrasound accuracy in, for example, the psoas compartment block,[34] sciatic nerve block,[35] facet joint injections,[36] and periradicular injections.[37] However, all these modalities have a limited resolution, which hinder an accurate determination of the various layers of nervous tissue, *i.e.* epineurium and perineurium.

There are some limitations to our study. Cryomicrotomy is the gold standard of choice for examining undisturbed topography of nerve structures. 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. A major limitation of cryomicrotomy is post-mortem examination of the tissue. This does not take into account the tissue oxygenation, blood circulation, and the elasticity of the structures in vivo. Although we tried to use fresh cadavers (within 12 hours post-mortem, unembalmed), factors such as elasticity of the skin, nervous and connective tissue, pulsatile arteries and tissue oxygenation cannot mimic the injection environment of a living person. Although the ultrasonographic difference of brachial plexus and sciatic nerve between cadaver en living subjects is reported to be minimal,[38,39] especially the post-mortem change in tissue elasticity in combination with needle handling could alter the echogenicity of the nervous structures.

Another important limitation of our report is the wide range of 95% confidence interval of the positive predictive values. The process of obtaining fresh cadavers and processing them with cryomicrotomy and histology is a time-consuming and complex work. This limits the inclusion and analysis of a large number of cadavers in a relatively short period. Nevertheless, the best available way of examining the anatomy without altering the structures, and the spread of the injectate is still the application of cryomicrotomy and histology as gold standard. In addition, we believe the values are still clinically significant and reflect reliable findings, as all lower limits of the 95% confidence intervals did not decline under 60%.

Finally, the reliability of the findings may be influenced by the choice of equipment: different ultrasound machines and needles could yield different findings.[40-42]

Under the conditions of our study, it is speculative to say whether intraneural injections caused structural damage to nerve fibers. In all intraneurally confirmed injections, evidence of dye inside the perineurium was found. It is unknown whether the staining of the perineural area was caused by diffusion or by puncture. The risk of direct structural damage to the perineurium is known to be low,[31] however, the degree of the associated neurologic dysfunction should be focus of further investigation.

In conclusion, ultrasound seems reliable to detect intraneural injection (up to 92% of attempts) confirmed with cryomicrotomy and histology. Expansion of the nerve in combination with change in the echogenicity is the most sensitive parameter of intraneural injection (positive predictive value of 94%).

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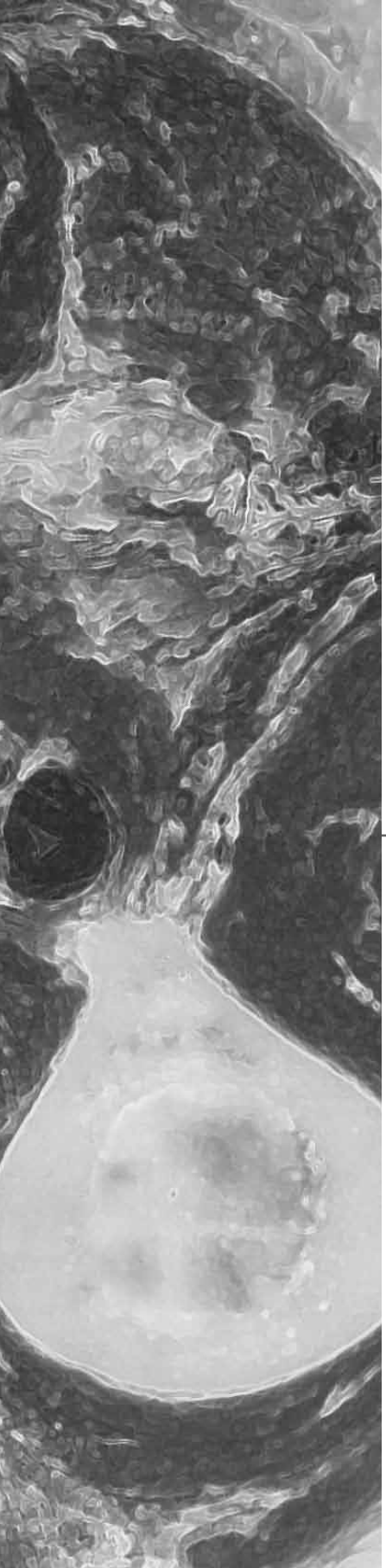

Chapter 11

General Discussion and Perspectives

Reliable localization of nervous structures is the first important step for a successful block. Often, a tool is used to facilitate the guidance of the needle towards the target, deep inside the body, using either a nerve stimulator or, increasingly, ultrasound. In this thesis electrical nerve stimulator for the vertical infraclavicular brachial plexus block *(chapter 2)* and ultrasound for the subgluteal sciatic nerve block *(chapter 3)* were discussed for their efficacy. However, even when these additional tools are used, a thorough knowledge of topographic anatomy of the nervous structures is needed. This is espacially true for ultrasound, in which the clinician is confronted with unfamiliar cross-sections. For this reason, reviews of the major block sites in arm and leg were presented *(chapters 4 and 5)*. Since the primary aim of peripheral nerve block is to position the local anesthetic around instead of inside the nervous structure, both tools were tested for their reliability to discriminate between intraneural and extraneural needle tip placement; the relation between intraneural injection and nerve damage was discussed; and a possible explanation for the observed differences or relationships was provided *(chapters 6 - 10)*.

In vertical infraclavicular brachial plexus block the needle is inserted as originally described by Kilka *et al.*[1] Its success is highly dependent on the type of motor response after stimulation, which depends upon which cord of the brachial plexus is stimulated. High success rates are found after stimulation of the medial or posterior cords, *i.e.,* distal flexor or extensor responses.[2-5] Thus, reinsertion or repositioning of the needle is necessary if, initially, a motor response that could be attributed to the posterior or medial cord, is not found. The consistent topographic pattern of the cords around the mid-infraclavicular area that we found, implies that, either the posterior or medial cord is located dorsal to the lateral cord, and that the medial cord lies just caudal to the posterior cord *(chapter 2)*. Furthermore, if the medial cord lies dorsal to the lateral cord, the posterior cord is always just cranial to the medial cord. As a consequence, the medial cord is located dorsocranial to the axillary artery. Thus, at this site, it is not located medial to the axillary artery, albeit the name of the cord would suggest a medial position relative to the axillary artery. This position is only reached further lateral.[6,7]

Based on these findings, we designed a simple algorithm to find the proper distal response in mid-infraclavicular brachial plexus blocks (Figure 1). It is based on the fact that, at the Doppler point, deeper parts (*i.e.*, posterior and medial cords) of the brachial plexus are reached by continuing the straight vertically inserted needle deeper, without deviating from its original course. Small deviations in any direction, which might occur unnoticeably, will result in relatively large displacements of the needle tip.[8] To place this in perspective, we conceived an intuitive rule, the *5-1-1* rule, which can be used up to angles of 30 degrees. It predicts that with a 5 cm needle, angulation of 1 degree deviates the needle tip with 1 mm at 5 cm depth. This implies that, for example, angulating a needle with 10 degrees (less than 2 minutes in an analogue clock) would displace the needle tip about 10 mm at 5 cm depth (Figure 2). Assuming that the cord sizes in the mid-infraclavicular area vary between approximately 5 and 8 mm, this could mean that even rather small angulations of the needle may result in bypassing one of the cords.

Although nerve stimulation is becoming less popular due to increased application of ultrasound, we think that algorithms such as described above will still be of help to clinicians who use electrical stimulation in their daily practice. They enable a more systematic approach in education and training and should reduce unnecessary redirections, which at present are usually based on trial and error.

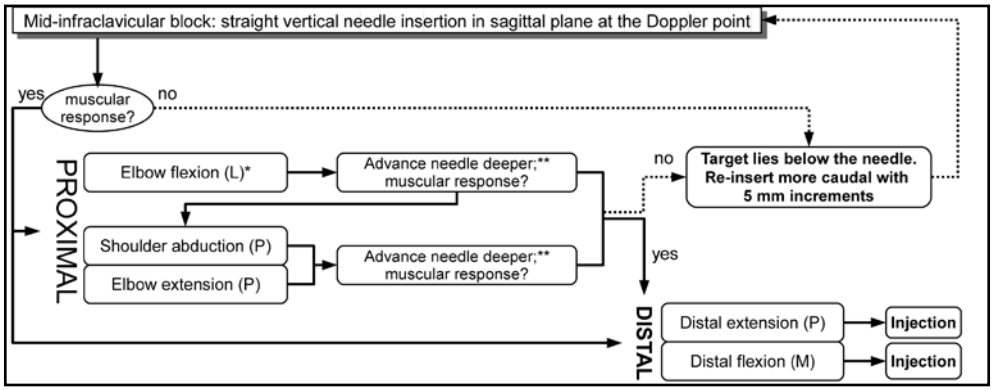

Figure 1. Redirection algorithm for mid-infraclavicular brachial plexus block to find the proper distal response. The needle is inserted at the Doppler-measured, maximum audible point of the sound of the axillary artery. The most frequently observed stimulation responses are used. *) Alternative responses *i.e.,* pronation or radial abduction of the wrist; **) Maximum depth of 5 cm. L lateral cord; P posterior cord; M medial cord.

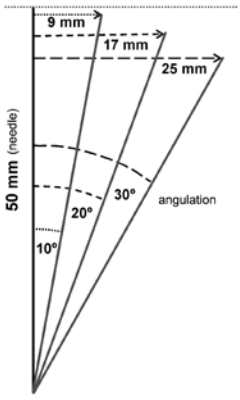

Figure 2. Geometrical representation of needle depth and the consequences of angulation. Based upon the co-sinus function, given the needle depth and the amount of angulation, the deviation is calculated. The amount of displacement of a 5 cm needle after an angulation of 10, 20 and 30 degrees is approximately 9, 17 and 25 mm, respectively. In the *5-1-1* rule, this is slightly overestimated by 10, 20 and 30 mm, respectively.

Having found the desired muscle twitch, however, does not guarantee a complete successful block. In VIB, after implementing our redirection algorithm, we found a success rate of 92%, reflecting a similar to higher success rate reported by other authors usingthe vertical infraclavicular technique.[9-12] In addition to the technical aspects, anatomic variations of the brachial plexus may prevent a 100% success rate, although the relevant anatomic variability may not be as high as generally presumed.

In addition to nerve stimulation, ultrasound has gained increasingly more popularity, although fast and clear identification of nerves may be challenging. Generally, arteries form a clear landmark, *e.g.*, the subclavian artery in ultrasound-guided supraclavicular brachial plexus block. For the sciatic block, such a landmark, however, is lacking. Therefore, we conducted an anatomic and clinical study to see if the proximal tendon of the long head of the biceps femoris (BFL) would be a soft tissue landmark for the identification of the sciatic nerve *(chapter 3)*. We found that the hyperechoic appearance of the BFL is a consistent, reliable and fast landmark for identification of the sciatic nerve; it was observed in 100% of the investigated volunteers.

Small differences are seen in the consistency and reliability of landmarks found for other regions of the sciatic nerve. In the midgluteal region for example, the sciatic nerve was identified in 95% of cases.[13] Differences in consistency between studies could be related to regional differences in the ultrasonographic imaging characteristics of the sciatic nerve, the investigated population, the use of nerve stimulation as gold standard, and also the experience of the anesthesiologist.

Furthermore, the application of ultrasound would have several distinct advantages. It would decrease procedural time, amount of local anesthetic and increase the effectiveness of the block.[14] However, sufficient experience and knowledge of the (sono)anatomy is needed to achieve these advantages. Because of the complex spatial configuration of the nervous structures, additional anatomic and histologic cross-sections are mandatory for interpretation of the ultrasound images. Other viewing planes than coronal, sagittal and transversal are often necessary to optimize image quality using a 90 degree angle of insonation to the nerves. This implies the need for anatomic cross-sections in varying planes, equivalent to those observed during ultrasonography. Therefore, we gave an extensive description of the major block sites of the brachial plexus *(chapter 4)* and of the sciatic nerve *(chapter 5)*, using parallel planes for ultrasound, anatomic cross-sections and histology.

A reliable identification of the deep nervous structures, either by electrical nerve stimulation or guided by ultrasound is a prerequisite for a successful nerve block. However, if the needle is near the target nerve, how can one be sure that the needle tip is not inside the nerve? Up to now, injection inside the nerve is considered to play a role in the development of neurologic complications. However, at present, the level of evidence of the exact relation between intraneural injection and nerve damage is unknown. Therefore, we conducted a systematic review to analyse all available data concerning this subject *(chapter 6)*. Two main outcomes are of particular interest: the difference between human and animal studies and the differences of application of the injectate inside or outside the fascicles. Roughly, in human studies, no increased risk for persistent nerve damage after intraneural injection was observed. This is in contrast to the animal studies, which usually found a strongly increased risk of nerve damage after application of local anesthetic inside the nerve. In our opinion, the main difference between human and animal studies is the difference in ability to detect the placement of the local anesthetic, *i.e.*, in animal studies, the investigators (presumably) were able to accurately inject either intrafascicularly or interfascicularly.[15-21] In contrast, in human studies, no such distinction could be made.[22-24]

In addition, injection inside the perineurium is associated with high injection pressures, which lead to fascicular injury and neurologic deficit, whereas injection inside the epineurium, but outside the perineurium, results in low initial pressures with no complications or acute return of normal motor function.[16,18] Further support for this phenomenon are the results from a recent study in rats, in which intraneural injection of ropivacaine at concentrations routinely used in clinical practice appeared to have no deleterious effect on sciatic nerve motor function.[17] Thus, it seems that an intraneural injection will not invariably cause neural damage, as long as it is outside the perineurium.

Furthermore, the site of injection seems to correlate with the risk of nerve damage. In a meta-analysis of the extent of neurologic dysfunction in peripheral nerve blocks, significantly more nerve injuries were seen in proximal blocks of the brachial plexus or sciatic nerve compared to the distal blocks.[25] This led to our hypothesis that the architecture

of the nerves could be relevant for the increased risk of nerve damage. Therefore, we investigated the quantitative architecture of both the brachial plexus *(chapter 7)* and the sciatic nerve *(chapter 8)*. We found that towards distal, the ratio of neural to nonneural tissue inside the nerve decreased in both nervous structures. This could explain the observed difference in risk of nerve damage between proximal and distal nerve blocks. If relatively more nonneural tissue is present, inadvertent intraneural (*i.e.,* intraepineurial) injection would be less damaging. This is in keeping with the data we found *(chapter 6)* for the human studies and would give support to the hypothesis that intraepineurial injection does not lead to an increased risk for persistent nerve damage. In proximal nerve blocks, the percentage of nervous tissue is higher, which would increase the risk of intrafascicular injection and, thus, nerve damage.

In addition, we speculate that the anatomic findings may have correlations with the onset time and the mean effective anesthetic volume of brachial plexus and sciatic nerve blocks. The larger mass of fat outside the nerves in the more distal regions might serve as a reservoir for lipophilic local anesthetics. Thus, the time needed to reach the neural tissue might be prolonged since less local anesthetic is available to diffuse across the epineurium to block the neural tissue. At the same time, from proximal to distal, the neural tissue is surrounded by an increasing amount of epineurial connective tissue. Thus, the local anesthetic will physically need more time to reach the fascicles, if it is not injected in the vicinity of the fascicles.

Indeed, studies have shown a larger volume of local anesthetic for the popliteal sciatic nerve block compared to the subgluteal approach.[28,29] Observational and interventional studies comparing proximal and more distal blocks of the sciatic nerve have also reported faster onset of sensory block in favor of proximal sciatic nerve block.[28,30,31] Even with less injected volume, a faster onset time and higher success rate were observed in a proximal approach compared to a more distal approach.[32]

Regarding the fact that toward distal more nonneural tissue and fat is found, it would be of interest to know which factor is more important to explain the disparities between the onset time and required volume of local anesthetic: neural/nonneural tissue distribution inside the nerve or fat around the nerve? Based on ultrasound studies, evidence suggests that less local anesthetic is needed for a reliable and successful nerve block compared to electrical stimulation-guided nerve blocks. For example, in a prospective randomized controlled trial, two times less local anesthetic was needed to block the popliteal sciatic nerve compared to nerve stimulation (17 *vs.* 37 ml, $P < 0.001$).[26] Very recently, only 1 ml of 2% lidocaine was needed for ultrasound-guided axillary block for each nerve.[27] Ultrasound is able to very accurately deliver local anesthetics next to the nerve, which is not possible when a nerve stimulator is used. Assuming the fact that in both techniques, local anesthetics are injected in the fat around the nerve, we believe that the distance to the nerve, but more importantly the amount of fat around the nerve, is the biggest reservoir of local anesthetic. Therefore, less fat around the nerve would make more local anesthetic available to diffuse to the nerve. In contrast, more fat around the nerve leads to higher uptake in the fat cells and small blood vessels in the fat compartment, which will physically delay the diffusion of local anesthetic to reach the nerves. All afore-mentioned factors would lead to a slower onset time and a requirement for larger doses of local anesthetic towards distal.

Unfortunately, no clinical studies have appeared up to now comparing onset time of

the same local anesthetic between proximal and distal nerve blocks. On the other hand, the differences in onset times could be masked due to the large amount of local anesthetics injected. One should take into account that large amounts of local anesthetic (up to 40 ml) are commonly used to achieve a reliable block. This large dose may mask the differences, which could be expected between proximal and distal approaches to the brachial plexus and sciatic nerve blocks.

Having established the risks of developing neurologic dysfunction and its possible anatomic explanation, the next important step should include prevention of intraneural injection. In this respect, nerve stimulation is believed to be safe if used within the generally advised range.[33,34] However, stimulating currents between 0.2 and 0.5 mA do not guarantee the proximity of the needle to the neural tissue.[35] Especially, it is unknown if the needle tip remains outside the confines of the nervous structures using these stimulation parameters. Therefore, we determined the minimally required stimulation threshold to elicit a motor response, outside and inside the brachial plexus during high-resolution ultrasound-guided, supraclavicular block *(chapter 9)*. Using ultrasound as gold standard, surprisingly, the generally advised range of stimulation threshold between 0.2 mA and no more than 0.5 mA was found in 54% of intraneurally positioned needle tips. Very recently, two human studies have also investigated the level of stimulation threshold inside the nerve and found similar results.[24,36] Moreover, the absence of motor response to nerve stimulation did not exclude intraneural needle placement. This may lead to additional unnecessary attempts in nerve localization. We can conclude that intraneural injection may be a common occurrence when used in combination with nerve stimulation. This is in keeping with recent findings in nerve stimulator-guided popliteal sciatic nerve block in which intraneural injection was observed in 66% and 83% of cases, none with nerve damage.[24,36]

A second important finding in this study is the need of higher stimulation thresholds for patients with diabetes mellitus. Although the included number of subjects was very low, the differences with nondiabetic patients were significant. Diabetes mellitus is becoming a widespread disease in our society. Thus, the issue if routine use of high stimulation thresholds should be advocated in diabetic patients, or that only ultrasound should be applied, or both, should be focus of future investigation.

A main limitation of this study and of recently published studies with similar results, however, is the accuracy of ultrasound to reliably detect intraneural injection. Although ultrasound is successfully used to exactly locate target nervous structures,[37,38] its limited resolution does not permit 100% reliability. This is also illustrated by the fact that most ultrasound-guided clinical studies report problems with obtaining satisfactory nerve images in a number of patients.[39,40] In our study, 31% of the investigated patients were excluded because of unclear ultrasound images, which did not permit reliable determination of intra- or extraneural needle position.

Still, since it is vital to detect intraneural injection, especially in the early phase when small volumes of local anesthetic are injected, it is essential to look for ultrasonographic characteristics that have a high accuracy and are consistent in detecting intraneural injection. Therefore, we conducted an anatomic study in which, using ultrasound, small volumes of dye (0.5 ml) were injected intraneurally in the supraclavicular brachial plexus and infragluteal sciatic nerve *(chapter 10)*. Cross-sections by cryomicrotomy were obtained to confirm or refute the presence of dye intraneurally. Increase in nerve surface area in combination with

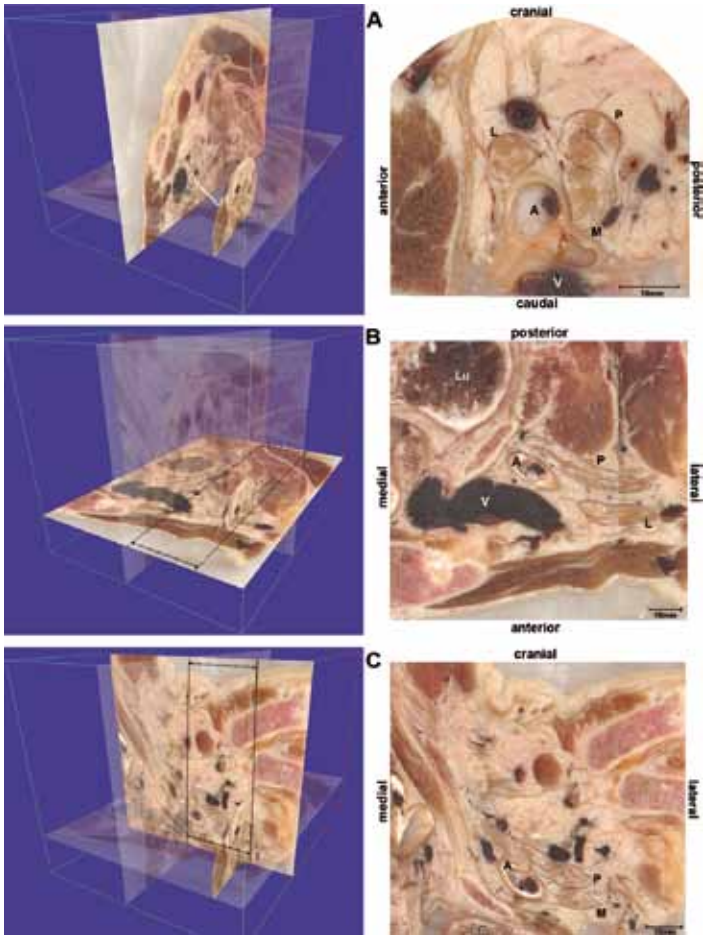

Figure 3. Reconstructions of the brachial plexus in the mid-infraclavicular area. A, axillary artery; V, axillary vein; L,P,M, lateral, posterior and medial cord; Lu, lung. **A**-left: reconstructed data cube with the most medial sagittal cross-section. Reconstructions were made in the trajectory of the white line from 5mm medial to 30mm lateral to the mid-infraclavicular point. **A**-right: brachial plexus perpendicular to its axis. **B**-left: reconstructed data cube with transversal cross-section through the brachial plexus. Black lines indicate the investigated area with interval of the measurements. **B**-right: detailed reconstructed transversal image of the brachial plexus. **C**-left: reconstructed data cube with frontal cross-section of the brachial plexus. Black lines indicate the investigated area with interval of the measurements. **C**-right: detailed reconstructed frontal image of the brachial plexus.

change in echogenicity was the most sensitive parameter after intraneural injection (94%). Even after injection of small amount of fluids, an increase of about 10% of nerve surface area could be observed. This permits detection of intraneural injection in the early phase, which – in theory – could decrease the risk of nerve damage. Less accurate characteristics included visualization of the needle tip and indentation of the nerve wall.

Anatomic studies on ultrasound-guided nerve localization blocks have reported comparable accuracy rates to exactly localize relatively small nerves, *e.g.*, lateral posterior cutaneous femoral, ilioinguinal and iliohypogastric nerves. However, these reports did not distinguish between intraneural or extraneural position of the needle tip.[37,41,42] In these studies, dissection was used to verify the location of the injected dye. We believe that this is not accurate enough, as dissection may disturb the local topography and spread of the injected dye and, as a consequence, will displace the exact location of the injectate and structures.

On the other hand, our applied gold standard, cryomicrotomy, leaves the topography undisturbed and allows for examination and measurement of dimensions and surfaces without altering topographic relations.[43,44] The obtained high-resolution images allow an

accurate analysis of the injected dye either intraneurally or extraneurally. Conventional imaging modalities such as computer tomography or magnetic resonance imaging are limited due to their resolution. A major limitation of cryomicrotomy is post-mortem examination, which does not take into account tissue oxygenation, blood circulation, and the elasticity of the structures in vivo. The effects of the muscle tone on the shape and diameter of the nervous structure are also diminished. In addition, shrinkage of tissue due to freezing is inevitable.[45]

However, the implementation of our digital anatomy with multiplanar reformating within the E-MAC program we developed, enables a unique combination of general overviews and highly detailed views of undisturbed anatomy of the major nerve block areas. Enlarged views enable a better comparison with and explanation of the internal echogenicity of the nerves. This may accelerate the learning curve of ultrasound-guided regional anesthesia (Figure 3). Furthermore, it can be easily implemented as additional training tool in regional anesthesia workshops.

Future Trends & Recommendations

This thesis presents new data about identification of target nervous structures, possible relation between intraneural injection and nerve damage, possible anatomic considerations for the risks of neurologic complications, onset time and minimal anesthetic local volume, and tools to prevent intraneural injection. As ultrasound is increasingly more applied, there is more need to objectively assess the risk of (unnoticed) ultrasound-guided intraneural injection and nerve damage. Therefore, further investigations are necessary to elucidate basic and clinical aspects of this issue. The following points need more attention:

- The extent of neurologic complications related to ultrasound-guided techniques. Evidence is becoming available about the superiority of ultrasound compared to conventional electrical stimulation-guided nerve localization. However, from the perspective of patient safety, little is known about the superiority of ultrasound compared with nerve stimulators.

- No data are available on the exact incidence of neurologic sequelae after peripheral nerve blocks. This requires a nation-wide survey about the distribution of complications among various techniques usually used in regional anesthesia and the equipment involved in nerve localization. The data of this survey will provide valuable information about how safe we really are in regional anesthesia.

- Data on the incidence of intraneural injection in both ultrasound-guided and nerve stimulation guided regional anesthesia are lacking. Although some studies have addressed this topic, they all were done in a very small size population, which does not permit extrapolation to the general population. Large population size incidence studies will objectively assess the incidence of intraneural injection and, as a consequence, provide valuable data if a relation exists between injection inside the nerve and the development of neurological dysfunction.

- To reach the highest level of evidence, randomized, controlled trials are necessary. There is evidence that intraneural disposition of local anesthetic leads to a successful block with almost immediate onset and adequate anesthetic and analgesic duration. Investigations should compare ultrasound-guided intraneural versus extraneural injection

with outcome measurements like block onset time, success rate of the block, quality of post-operative analgesia, patient satisfaction and number of nerve damage events.

- Our data about extraneural versus intraneural stimulation thresholds suggests that patients with diabetes mellitus need higher stimulation thresholds to elicit muscle contractions during nerve stimulator-guided nerve blockade. This is based on observational data with a very small size of patients. Because diabetes mellitus is increasingly becoming wide-spread in society, our observations need to be verified in a much larger population of patients with diabetes mellitus. Large randomized trials are needed to objectively assess the optimal stimulation threshold for diabetic patients, or to determine if ultrasound, or the combination of ultrasound and electrical stimulation, is more safe *and/or* effective.

- Available correlative studies between ultrasound and in vivo anatomy of nervous structures are based on relatively outdated technology. Advances in technology necessitate revision of our current understanding of the sonoanatomic architecture of the nerves. The data obtained by cryomicrotomy and the E-MAC program should be implemented in training programs for regional anesthesia.

- Little is known about the architecture of the nervous tissue in affected individuals. Diseases like diabetes mellitus, leprosy and various polyneuropathies not only affect the function but also the structure of the nerve. Evidence is lacking about the value of ultrasonography in diagnosis of such diseases.

Conclusions

1. In vertical infraclavicular block, stimulation of either the posterior or medial cord is associated with the highest success rate. To reach these cords, we developed an algorithm which predicts the redirection of needle. Once lateral cord stimulation is elicited, a further (*i.e.* deeper) advancement of the needle will result in the proper distal motor response.

2. In sciatic nerve block, hyperechoic tendinous fibers of the long head of the biceps femoris are a reliable soft tissue landmark for a fast and reliable ultrasound localization of the infragluteal sciatic nerve.

3. With regard to the brachial plexus and sciatic nerve: A detailed correlation of reconstructed, cross-sectional gross anatomy and histology with ultrasound sonoanatomy helps the clinician to better understand their topography and internal architecture. It will increase the actual knowledge of relevant anatomy during ultrasound-guided nerve blocks.

4. Injection of local anesthetics inside the fascicles of a nerve (intrafascicular injection) is highly associated with nerve damage. However, injection outside the fascicles (interfascicular injection) might not cause any neurological dysfunction.

5. High injection pressure, which is also associated with intrafascicular injection, is highly associated with the development of nerve damage.

6. In the brachial plexus, the amount of nonneural tissue both inside and outside the nerves increases from proximal to distal. This observation may explain why injections within the epineurium may not invariably result in neural injury. It may also affect onset times of brachial plexus blocks.

7. In the sciatic nerve, the amount of nonneural tissue both inside and outside the nerves increases towards distal. This may suggest a higher vulnerability for neurological sequelae in proximal sciatic nerve blocks, and may explain differences observed in minimal local anesthetic volume and onset time between proximal and distal sciatic nerve blocks.

8. In supraclavicular, ultrasound-guided brachial plexus block, a stimulation threshold of 0.2 mA or less is reliable to detect intraneural placement of the needle. However, stimulation thresholds of more than 0.2 and no more than 0.5 mA do not rule out intraneural position.

9. Expansion of the nerve combined with change in echogenicity is the most sensitive ultrasound parameter for an early detection of intraneural injection. Already small volume injections inside the nerve can thus be assessed.

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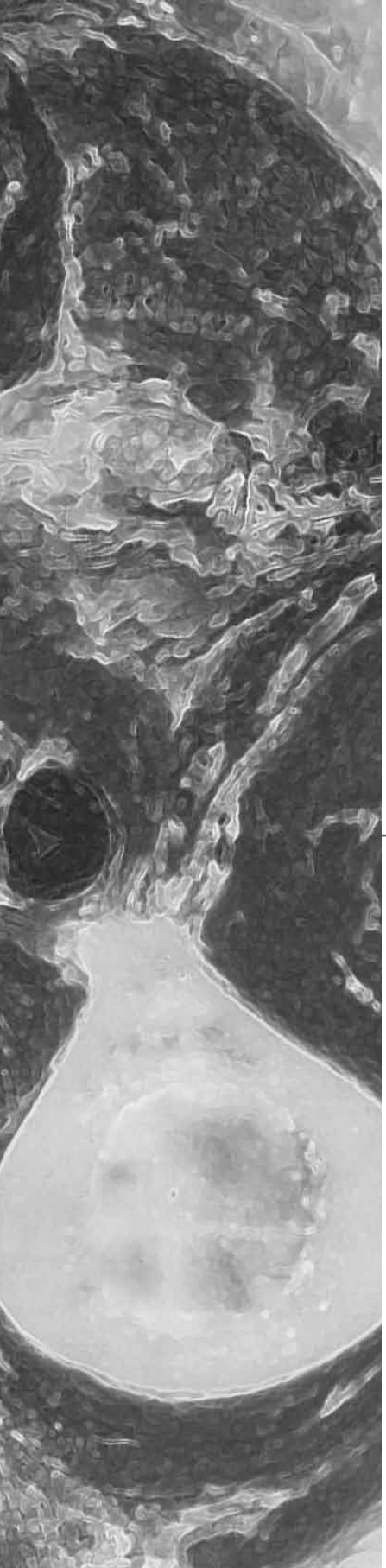


Summary

This thesis deals with the following topics: 1. techniques to reliably identify nervous structures, 2. possible relation between injection of local anesthetics inside the nerve and nerve injury, 3. anatomic explanation for the differences seen in neurologic complications between proximal and distal nerve blocks, and, finally, 4. ways to early detect injection of local anesthetics inside the nerve. These issues are investigated for the most frequently blocked nervous structures: the brachial plexus (arm) and the sciatic nerve (leg). To identify nerves of the brachial plexus and the sciatic nerve techniques, such as nerve stimulation and ultrasound are used. The first chapters of this thesis *(chapters 2 to 5)* deal with nerve identification techniques using electrical nerve stimulation and ultrasound. The following chapters *(6 to 10)* deal with factors related to nerve injury after intraneural injection. The findings of this thesis are further discussed in the last chapter and recommendations are given for future focus and research. This summary is continued with highlights of each chapter in this thesis.

In chapter 1, an introduction is given about the history of tools applied for identification of nervous structures inside the human body. Further, our current understanding on the reliability of electrical nerve stimulation and ultrasound to diagnose injection inside the nerve is highlighted. The need for further investigation is explained and the aims of the thesis are formulated.

In chapter 2, we describe the technique of vertical infraclavicular block to adequately anesthetize the brachial plexus. When the results of the anatomic study were implemented, in the clinical study, the success rate to reach deeper parts of the brachial plexus, *i.e.,* medial and posterior cord, after eliciting a lateral cord stimulation was 98%. This is achieved by inserting the perpendicular inserted needle deeper to a maximum of 50 mm. The surgical success rate of this technique is 92%.

Chapter 3 describes identification of the infragluteal sciatic nerve using consistently visible and easy identifiable soft tissue, which was verified in an anatomic study. The results show that the hyperechoic (white) structure at the medial border of the long head of the biceps femoris tendon might be a reliable soft tissue landmark for fast ultrasound localization of the infragluteal sciatic nerve.

In chapter 4 and 5, an extensive overview is given about the sonoanatomy of the brachial plexus and the sciatic nerve. In these reviews, imaging modalities such as cross-sectional anatomy, histology and ultrasonography are combined. The (sono)anatomic features of these nervous structures are described at the major block sites. For both nervous structures, the three imaging modalities were exactly matched, thus enabling a unique comparison and explanation of the ultrasound images. This was done for the brachial plexus in the interscalene, supraclavicular, infraclavicular and axillary region, and for the sciatic nerve in the midgluteal, infragluteal, midfemoral and popliteal region.

In chapter 6, we conducted a systematic review on the relation between injection of local anesthetics inside the nerve and neurologic sequelae. Animal as well as human studies were analyzed. A discrepancy was found between human and animal studies. Animal studies, usually older studies, tend to find an increased risk of nerve damage after intraneural (specifically intrafascicular, *i.e.,* inside the perineurium) injection. In addition, a strong correlation was seen between intrafascicular injection, high injection pressure and nerve damage. Human, more recent studies, tend to find no delirious effect of intraneural injection, both intentionally or unintentionally. As in all systematic reviews, an important

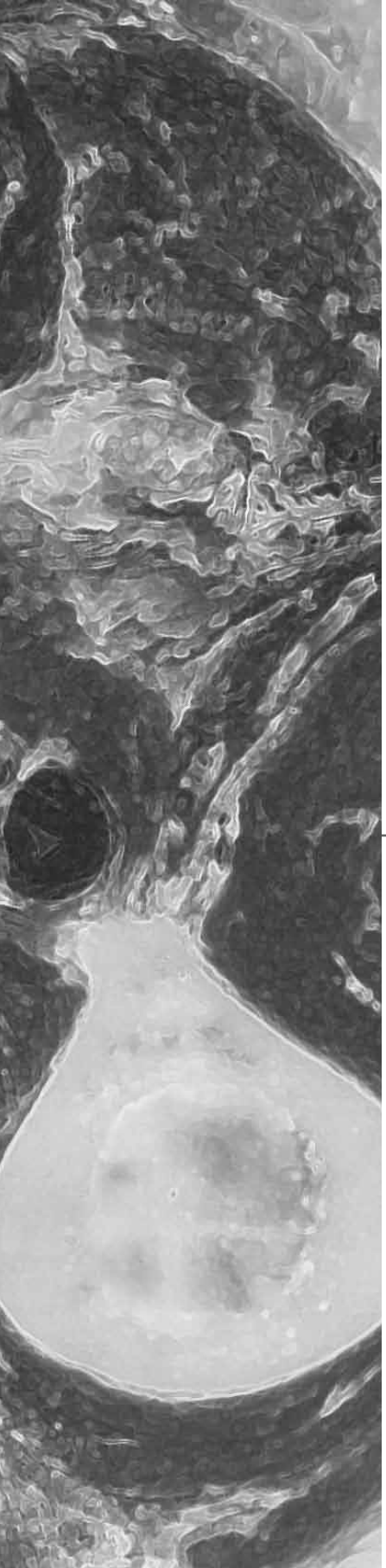
limitation of this systematic review was the lack of homogeneity, *i.e.,* the use of different kinds and volumes of local anesthetics, the use of different needles, and the diversity in the patient population.

In chapter 7 and 8, a quantitative analysis was done of the internal architecture of the brachial plexus and the sciatic nerve. Using cryomicrotomy to preserve the topographical relations of the structures, cross-sections with an interval of 78 μm were obtained from human cadavers. Using specially developed software (Enhanced Mutiplanar reformatting Along Curves software, E-MAC©) reconstructions were made perpendicular to the long axis of the nervous structures. Differences were found between the neural and nonneural tissue components in the proximal and distal regions of the brachial plexus as well as the sciatic nerve. The nonneural tissue (stroma and connective tissue) inside and outside the nervous structures increased from proximal to distal. The ratio neural : nonneural tissue inside the nerve increased from 1:1 in the proximal to 1:2 in the distal regions of the brachial plexus. For the sciatic nerve, this ratio changed from 2:1 to 1:1. In both brachial plexus and sciatic nerve, the adipose tissue compartment outside the nerves increased significantly towards distal. All these differences in neural architecture and size of surrounding adipose tissue compartments may explain why some injections within the epineurium do not result in neural injury, and affect onset time and mean effective anesthetic volume required for a successful block.

In chapter 9, the hypothesis was tested whether nerve stimulation is reliable enough to distinguish between intraneural and extraneural environment. The findings revealed that stimulation thresholds between 0.2 and 0.5 mA are seen both inside and outside the nerve, *i.e.,* in 54% of cases intraneurally and in 41% extraneurally. On the other hand, stimulation thresholds less than 0.2 mA were not found extraneurally. Diabetic patients required higher stimulation thresholds to elicit a motor response, both outside and inside the nerve.

In chapter 10, we investigated the consistency of ultrasound to early detect injection of local anesthetic inside the supraclavicular brachial plexus and sciatic nerve. Using fresh cadavers, intraneural injections were performed according to predefined criteria. Cryomicrotomy and histology were used as gold standards. This anatomic study showed that with ultrasound already small volume (0.5 ml) intraneural injection into the brachial plexus and sciatic nerve (up to 92% of cases) can be reliaby detected. The combination of expansion of the nerve and change in echogenicity was the most sensitive parameter of intraneural injection. Ultrasound could therefore be regarded as a reliable tool to early detect intraneural injection during nerve blocks.

Finally, in chapter 11, we summarize and discuss the findings presented in this thesis. Our findings are reflected in light of the available evidence in literature. For future focus, a set of recommendations are given, and final conclusions are drawn.



Samenvatting

Bij chirurgische ingrepen aan arm of been verdient locoregionale anesthesie de voorkeur. Redenen daarvoor zijn het gemak van de techniek, betrouwbare en efficiënte pijnbestrijding zowel tijdens als na de operatie, snelle revalidatie en, tenslotte, betere kostenbeheersing vanwege een korter ziekenhuisverblijf. Dit proefschrift beschrijft een tweetal technieken waarin het zoeken en vinden van de zenuwstructuren centraal staat, t.w. elektrische stimulatie van zenuwen en ultrasound (echo; een techniek waarbij met behulp van geluidsgolven zenuwen zichtbaar gemaakt kunnen worden). Daarnaast wordt door middel van anatomisch onderzoek bekeken in hoe verre de samenstelling van de zenuwen de kans op zenuwschade beïnvloedt. Daarbij zal ook de rol van deze hulpmiddelen onderzocht worden. Het eerste deel van dit proefschrift *(hoofdstukken 2 tot en met 5)* behandelt de technieken waarmee zenuwstructuren door middel van zenuwstimulatie en echo zo betrouwbaar mogelijk geïdentificeerd kunnen worden. Omdat het de bedoeling is de lokale verdovingsmiddelen *rond* de zenuwen te plaatsen en niet *in* de zenuwen, wordt in de rest van het proefschrift *(hoofdstukken 6 tot en met 10)* onderzocht in hoeverre het mogelijk is om injecties in de zenuwen te identificeren en mogelijk te voorkomen. Daarbij zal ook de relatie worden onderzocht tussen de relatieve hoeveelheid netto zenuwweefsel in een zenuw en de kans op het optreden van zenuwschade. Deze samenvatting zal alle hoofdstukken kort belichten.

In hoofdstuk 1 wordt een algemeen introductie gegeven over de geschiedenis van het gebruik van hulpmiddelen om zenuwstructuren binnen de locoregionale anesthesie te identificeren. De aandacht richt zich enkel op zenuwstimulatie en echo, de twee meest gebruikte hulpmiddelen voor het plaatsen van injecties rond zenuwen. De noodzaak van verder onderzoek wordt toegelicht, waarna de doelstellingen van dit proefschrift worden uiteengezet.

In hoofdstuk 2 beschrijven we een techniek die gebruikt wordt bij het verdoven van de arm, namelijk de verticale infraclaviculaire blokkade van de plexus brachialis. Het onderzoek omvat zowel een anatomisch als klinisch gedeelte waarin de vraag wordt beantwoord in hoeverre er een algoritme te bedenken is om de diepere gedeeltes van de plexus brachialis (fasciculus medialis en posterior) betrouwbaar, snel en efficiënt te bereiken en te verdoven nadat het oppervlakkige gedeelte (fasciculus lateralis) eenmaal is gevonden. De resultaten van het onderzoek geven aan dat volgens ons algoritme in 98% van de gevallen de diepere gedeeltes van de plexus brachialis gevonden kunnen worden. Dit leidt tot een betrouwbare blokkade van de zenuwen in 92% van de gevallen zonder het optreden van complicaties.

In hoofdstuk 3 beschrijven we een nieuwe echografische techniek om de grootste zenuw van het lichaam, de nervus ischiadicus, zo snel en efficiënt mogelijk te identificeren. Ook hier zijn de resultaten van zowel het anatomische als klinische werk samengevoegd. Na analyse van de data bleek dat de hyperechogene (witte) structuur aan de mediale zijde van de lange kop van de biceps femoris (onderdeel van de hamstrings) een consistente structuur is om de nervus ischiadicus betrouwbaar en snel te identificeren.

In hoofdstukken 4 en 5 wordt een uitgebreide beschrijving gegeven van de sonoanatomie (= echo-anatomie) van de plexus brachialis en de nervus ischiadicus. In deze twee reviews worden anatomie, histologie en echo gecombineerd. De sonoanatomische eigenschappen van de zenuwstructuren worden beschreven in het kader van hun interne architectuur, ligging (topografie) en verloop, vanaf proximaal tot distaal. Hierbij ligt de focus op de relevante regio's die vaak worden gekozen bij het verrichten van blokkades in het schouder-

en bovenbeengebied. De echobeelden van de zenuwstructuren werden gematcht met hun corresponderende anatomische en histologische beelden, in exact hetzelfde gebied en onder dezelfde hoek. Dit leidt tot unieke beelden die de duiding van de echobeelden aanzienlijk vereenvoudigen en bijdragen tot het vergroten van de actuele parate anatomische kennis tijdens het uitvoeren van de blokkades.

In hoofdstuk 6 wordt de relatie tussen injectie van een lokale verdovingsvloeistof in de zenuw en het risico op het optreden van zenuwschade vastgesteld volgens een gestandaardiseerd overzicht (systematic review). Na bestudering van de gevonden studies blijkt dat dierexperimentele onderzoeken vaker een relatie vinden tussen injectie in de zenuw (specifiek in het perineurium van de zenuw) vergeleken met humane studies. Tevens blijkt dat hoge druk tijdens injecties een hoge correlatie kent met zenuwschade. Een van de belangrijkste beperkingen van het review is het gebrek aan uniformiteit tussen de studies waardoor vergelijkingen tussen de specifieke effecten van verschillende factoren zeer lastig wordt.

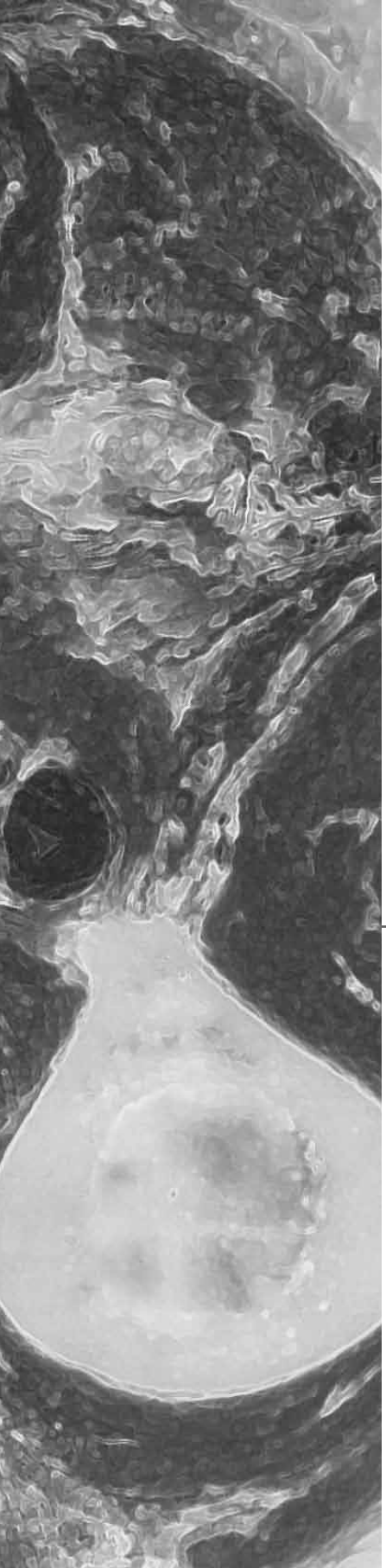
In hoofdstukken 7 en 8 worden (micro-)anatomisch onderzoek verricht naar de kwantitatieve architectuur van de plexus brachialis en de nervus ischiadicus. Hierbij worden door middel van cryomicrotomie hoge resolutie dwarsdoorsneden met een interval van 78 micrometer van het menselijke lichaam vervaardigd en gefotografeerd. Na analyse en meting blijkt dat het percentage zenuw/vetweefsel in de zenuwen van zowel plexus brachialis als nervus ischiadicus significant afneemt naar mate de zenuwstructuren dichter bij de doelorganen komen. De zogenaamde ratio zenuw/vetweefsel in de zenuwen neemt af. Voor de plexus brachialis is deze ratio 1:1 in de nek (proximaal) en 1:2 in de schouder (distaal). Voor de nervus ischiadicus is deze ratio 2:1 in het bilgebied (proximaal) en 1:1 in het kniegebied (distaal). Tevens neemt de hoeveelheid vet buiten de zenuwen significant toe naarmate de zenuwen verder van de wervelkolom afliggen. Dit heeft gevolgen voor het risico op het ontstaan van zenuwschade (proximaal hoger dan distaal), de hoeveelheid verdovingsvloeistof (proximaal lager dan distaal) en de snelheid van het begin van de verdoving (proximaal sneller dan distaal).

In hoofdstuk 9 wordt de hypothese getoetst in hoeverre zenuwstimulatie betrouwbaar is om intraneurale (in de zenuw) van extraneurale (buiten de zenuw) injecties te kunnen onderscheiden. Na stimulatie van de zenuwstructuren zowel binnen als buiten en bevestiging van de positie van de stimulatienaald door middel van echo, blijkt dat de gangbare stroomsterkte tussen 0.2 en 0.5 mA onbetrouwbaar is om de positie van de naald ten opzichte van de zenuwstructuur te bepalen (vergelijk: intraneuraal in 54% en extraneuraal in 41% van de gevallen). Daarnaast blijkt dat stroomsterktes lager dan 0.2 mA wel degelijk betrouwbaar zijn voor intraneurale positie van de naald. Patiënten met suikerziekte hebben significant hogere stroomsterktes nodig voor zowel intraneurale als extraneurale stimulatie van de zenuwen. Concluderend is zenuwstimulatie slechts geschikt voor detectie van intraneurale injectie indien een spiersamentrekking opgewekt kan worden met een stroomsterkte van 0.2 of lager.

In hoofdstuk 10 wordt de nauwkeurigheid van echo onderzocht om injecties van vloeistoffen in de zenuwen vroeg te kunnen identificeren. Door middel van echo werd in zowel de plexus brachialis als de nervus ischiadicus intraneuraal 0.5 ml kleurstof geïnjecteerd. De echobeelden werden vervolgens geanalyseerd aan de hand van voorgedefiniëerde echo-karakteristieken die worden waargenomen bij intraneurale injecties. In 94% van de

gevallen werd de vloeistof daadwerkelijk in de zenuw aangetroffen. Vergroting van het zenuwoppervlak gecombineerd met verandering in het echobeeld (meer zwarting in de zenuw) geldt als belangrijkste indicator voor intraneurale injectie (92%). Concluderend kan echo gezien worden als een betrouwbaar hulpmiddel voor vroege detectie van kleine hoeveelheden injectievloeistof in de zenuw.

Tenslotte worden in hoofdstuk 11 alle voorgaande hoofdstukken samengevat en bediscussieerd in het licht van de beschikbare bewijs in de literatuur. Aan de hand daarvan worden aanbevelingen gegeven voor toekomstig onderzoek en worden eindconclusies geformuleerd.



موجز الرسالة

لقد ثبت علميا ان التخدير الموضعي الذي يستخدم عند العمليات المتعلقة بالاذرع او الارجل أفضل من التخدير العام. ومن اهم الأسباب المتعلقة بذلك هي اولا: سهولة اجراء التخدير للعملية، ثانيا: تحقيق افضل النتائج من ناحية تخفيف الآلام على المريض أثناء العملية وبعدها، ثالثا: التأهيل السريع للمريض بعد الجراحة بمعنى مغادرة المريض المستشفى بعد العملية مباشرة، والنقطة الرابعة والأخيرة هي الافضلية من الناحية الاقتصادية للمريض من حيث التكلفة. وفي هذا الإطار، تصف هذه الرسالة التي بين ايديكم، تقنيات لبحث وتحديد الهياكل العصبية في الكتف واعلى الرجل من خلال استعمال آلالات الخاصة كالمحفز الكهربائي (الصعقة الكهربائية) او جهاز السونار. بالإضافة إلى ذلك، تحتوي هذه الرسالة على فصلين مع شرح مفصل حول تركيبة الاعصاب ورأيتها من خلال جهاز السونار.

الجزء الأول من هذه الرسالة التي تحتوي الفصول الثاني الى الخامس تتناول تركيبة وتحديد الهياكل العصبية عن طريق الموجات فوق الصوتية (السونار) والمحفز الكهربائي (الصعقة). اما في الجزء الثاني الذي يحتوي الفصول السادس الى العاشر سوف نتعمق في مدى خطورة وقوع اي ضرر بعد حقن الاعصاب بالمخدر. الى جانب ذلك تمكنا من معرفة التركيبة الداخلية للاعصاب في ما يخص الاضرار الخاصة بالتخدير. واخيرا، سوف نتطرق الى امكانية التجنب من حقن داخل العصب من خلال استعمال المحفز الكهربائي أو السونار.

سوف نتطرق بشكل موجز حول الفصول التالية:

الفصل الاول مقدمة عامة عن تاريخ الوسائل المستعملة لبحث وتحديد الاعصاب في مجال التخدير الموضعي. وفي هذا الايطار سوف نتطرق لفوائد استعمال المحفز الكهربائي والسونار، الجهازين الاكثر استعمالا في هذا المجال. ايضا سوف نتطرق للحاجة الماسة للابحاث التي تجدونها في هذه الرسالة، مع ذكر الفرضيات العلمية والاهداف من ذلك.

اما في الفصل الثاني سوف نتطرق الى طريقة التخدير العمودي تحت عظم الترقوة لتخدير الذراع من خلال تخدير اعصاب الضفيرة العضدية. وتتكون هذه الدراسة من جزئين: الجزء التشريحي والسريري. هذا وقد تم البحث عن سبل تحديد الاعصاب العميقة للشبكة العصبية تحت العضم الترقوة. وتشير النتائج التي توصلنا لها بعد تحديد الجزء السطحي من شبكة الاعصاب، انه يمكن تحديد الاجزاء الاعمق للشبكة العصبية ومن ثم تخديرها من خلال ادخال الابرة بشكل اعمق بدون انحراف. وهذه الطريقة تؤدي الى تحديد الاجزاء العميقة من الشبكة العصبية في 98% من الحالات. وسوف تؤدي الطريقة الى تخدير 92% من الاشخاص من دون وقوع اي مضاعفات.

وفي الفصل الثالث يتم شرح طريقة جديدة لاستعمال السونار لتخدير اكبر عصب في جسم الانسان الذي يسمى (العصب الوركي) الواقع في الرجل. وهذه البحث يتكون من جزئين تشريحي وسريري. حيث اظهرت البيانات أن ما يرى في السونار من هيكل ابيض اللون هو الجزء الوسطي من رباط العضلة ذات الرأس الطويل الذي يقوم بتحديد العصب الوركي بشكل سريع ودقيق وثابت في 100% من الحالات.

وفي الفصلين الرابع والخامس نقوم بشرح مفصل حول التركيبة العصبية للضفيرة العضدية والعصب الوركي من خلال التشريح للاعصاب والانسجة وكيفية التعرف عليها بجهاز السونار. وهناك ايضا شرح مفصل للاعصاب في سياق الهيكل الداخلي والطبوغرافي حيث يتم التركيز على مناطق ذات اهمية في علم التخدير والتي غالبا ما يتم اختيارها لوضع المخدر في الكتف والفخذ. كما نقوم بمشاهدة وشرح الاعصاب من خلال السونار ومطابقة هذه الصور للصور التشريحية و النسيجية المحددة في نفس المنطقة والزاوية.

في الفصل السادس، قمنا بإجراء استعراض وتحقيق شامل في ما يوجد من بحوث حول خطر وقوع إصابات بالاعصاب بعد حقنها بالمخدر. فقد شمل البحث جميع الدراسات المختصة بالبشرية والحيوانية على حد سواء. واثبتت النتائج المستخلصة للبحوث

والدراسات الحيوانية ان الاعصاب قد تصيب باضرار كبيرة بعد عملية التزريق لها ووقوع تغيير سلبي بهيكلية الاعصاب. وبتوضيح اكبر ان خطر وقوع الاضرار يزداد كثيرا بعد حقن المخدر في الغلاف الداخلي للاعصاب والذي يحتوي على الالياف العصبية، كما ان نسبة الخطر تزداد عندما يتم التزريق تحت ضغط عالي. وعلى العكس من ذلك، لم تظهر الدراسات البشرية النتائج السلبية على الاعصاب مقارنتا بالدراسات الحيوانية. وقد تكمن الاسباب في ذلك ان هذا التفاوت يعود بغياب التجانس بين الدراسات والظروف المختلفة في الاساليب والاصناف المدروسة.

في الفصلين السابع والثامن، يتم دراسة البنية الاساسية للعصبين الرئيسيين في الذراع والساق (الضفيرة العضدية والعصب الوركي). فقد قمنا بقياس المحتوى الداخلي للعصب من حيث نسبة الانسجة العصبية واللاعصبية من خلال اخذ شرائح رفيعة جدا (87 مكرومتر) من العصب ابتداءا من الرقبة الى اقصى الكتف بالنسبة للذراع ومن العضلة الكمثرية في الحوض الى المأبض (منطقة الركبة) بالنسبة للساق. فقد بينت النتائج الاولية ان نسبة الانسجة العصبية مقارنة بالانسجة اللاعصبية تنخفض خلال مسار العصب حيث تكون هذه النسبة 50% وتصبح 33% في الضفيرة العضدية خلال مسارها الى الكتف، اما النسبة للساق تبدأ بـــ 66% وتصبح 50% في مسارها الى الاسفل. كما ان كمية الدهون خارج الاعصاب تزداد بشكل ملحوظ كلما اوشك العصب الى الانتهاء. هذه النتائج ربما تؤثر على احتمال وقوع اضرار على العصب، كما تؤثر على الكمية المستخدمة للمخدر، وسرعة استجابت العصب للمخدر.

في الفصل التاسع، اختبرنا فرضية استعمال المحفز الكهربائي لتحديد الفضاء الداخلي والخارجي للعصب. فقد قمنا بتحديد موقع رأس الابرة بالسونار بعد خفض قوة التيار الكهربائي. تبين بعد فحص النتائج ان قدرة التيار الكهربائي ما بين 0.2 و 0.5 ميلي أمبير والتي هي نفس القدرة المستعملة عادة، لا يمكن الاعتماد عليها في تحديد الفضاء الداخلي عن الفضاء الخارجي من العصب. اما قدرة التيار الكهربائي التي تقل عن 0.2 ميلي أمبير تحدد بدقة الفضاء الداخلي للعصب. اما بالنسبة لمرضى السكري فإن هناك ارتفاع لمستويات القدرة الكهربائية لتحديد الفضاء الداخل والخارجي للعصب.

في الفصل العاشر، قمنا بفحص دقة جهاز السونار لحقن كميات صغيرة من السوائل داخل العصب. بعد تحديد موقع الاعصاب في الكتف والساق تم حقن كمية صغيرة من السائل (مثيلين بلو 0.5 مل) داخل فضاء العصب بنائا على معالم بصرية للسونار. وتأكدنا من موقع السائل من خلال تحليل الصور التي اخذت من موقع الحقن تحت المجهر. واكدت النتائج في ٪94 من الحالات وجود السائل داخل فضاء العصب. والمؤشر الاكثر دقة للتأكد من الحقن الداخلي للعصب هو الزيادة المرئية لحجم العصب مع تغيير ملحوظ في اللون على شاشة السونار والذي شوهد في ٪92 من الحالات. لذلك جهاز السونار دقيق باعتباره وسيلة يعتمد عليه للكشف المبكر عن وجود كميات صغيرة من السائل داخل فضاء العصب.

وختاما في الفصل الحادي عشر، تمت مناقشة جميع البحوث والدراسات في هذه الرسالة لاقصى ما توصل له البحث العلمي. وبناء على هذا الأساس، نقوم باعطاء توصيات للمستقبل من أجل البحث عن طرق جديدة لتطوير كيفية استعمال جهاز السونار في خفض نسبة المضاعفات على الاعصاب.

شرح مختصر حول الكاتب: الدكتور نزار المعيري من مواليد سنة 1980م (النجف الاشرف، عراق). اكمل دراسة الطب في جامعة اوترخت الهولندية في عام 2007 وحصل من نفس الجامعة على شهادة الدكتوراة في سنة 2010 بنائا على الرسالة العلمية التي بين ايديكم.

بحمد الله وعونه وتوفيقه تم اعداد وكتابة هذه الرسالة بفضل وبركة منه.

كانون الثاني/يناير 2010 المصادف محرم 1431

Dankwoord

Een razend snelle trein: zo wil ik mijn leven kenmerken. Promotie is een belangrijk tussenstation in een leven met veel schakels. Een tussenstation dat soms tot onbekende gebieden leidt. Een tussenstation dat soms tot onbekende mensen leidt. Zo leer ik dat het spoorboekje niet heilig is, dat creativiteit en structuur, hart en verstand, geluk en lot onafscheidelijk met elkaar zijn verbonden. Zonder de ingenieur, de trein, de machinisten, de hoofdconducteur en de medereizigers heeft het reizen geen smaak. Het doel doet vermoeidheid vergeten. Dat maakt het resultaat nog zoeter. Dat maakt mijn dankbetuiging nog gewichtiger…

Alom aanwezig, hier, daar en overal, voor en na de tijd, levend, niet aanwijsbaar, niet begrensbaar: mijn eeuwige dank dat U het mij heeft mogelijk gemaakt.

Dr. Groen, beste Gerbrand: ik zou niet overdrijven als ik zeg dat zonder je inzet dit proefschrift nooit tot stand zou zijn gekomen. Je scherpe, kritische en analytische vermogens -al dan niet in combinatie met receptoren verzadigd met tabak- om stukken te corrigeren is bewonderenswaardig. Al sinds mijn studie heb ik je gekend als docent, wetenschapper en bovenal als mens. In het begin was het erg onwennig voor mij: ik, nog een ukkie, die de eer heeft met een doorgewinterde academicus samen projecten te bedenken, uit te voeren en tot een goed eind te brengen. De periode samen met jou, heeft niet alleen in wetenschappelijke zin meer dan verwacht haar vruchten afgeworpen. Ook als mens hebben wij beiden de zekere ontwikkeling meegemaakt. Ik kan in dit opzicht over mezelf spreken. Je wijze levensverhalen tussen alle hectiek door waren voor mij een ware inspiratiebron. De kleren van de keizer, Abel en Caïn, de zegen van de heilige Blasius, de verhalen over de "veranda", en je onnavolgbare kunsten om computers helemaal om te leggen, om maar eens een paar voorbeelden te noemen. Maar bovenal de gebruikelijke YES "... we can" als weer eens een artikel werd geaccepteerd. En dat hebben we gelukkig vele malen mogen en kunnen herhalen. Rest nog je motto maar eens te herhalen: "Een dag niet gelachen is een dag niet geleefd". Hoe kan het ook anders als je kamer een oase is voor menig student waar hartelijk gelachen kan worden…

Geachte prof. Kalkman, beste Cor: nog tijdens mijn studie heeft Gerbrand mij in contact gebracht met u. Ik ben het nog niet vergeten toen u aanbood mij te begeleiden bij een eventuele promotie toen ik nog in de schoolbanken zat. Na wat wikken en wegen en via zijpaden kwam ik bij u terecht. Met voldoening kan ik zeggen dat mijn keuze voor promoveren een zeer goede, zo niet de beste keuze was geweest in mijn leven tot nu toe. Onze gesprekken waren kort, maar krachtig. Uw interesse en geloof in mij, zowel als mens, maar ook als promovendus, waardeer ik zeer en zullen mij tot de rest van mijn leven bijblijven. Uw positieve instelling en uw kritische kijk op het geheel werken motiverend. Ik hoop in de toekomst nog veel met u samen te werken via andere wegen.

Dear dr. Bigeleisen, dear Paul: I wouldn't exaggerate if I would say that my research project in Pittsburgh, PA, funded by the Fulbright Foundation, to whom I am very grateful, lay the foundation for this thesis. What we achieved during the project would cost others years to achieve. I have known you as a brilliant scientist, but most importantly as a loving husband of Laurie, with whom I still remember our conversations about world politics. It is a privilege having known you and your family and I am still honoured having worked with

you. I hope we continue working together on more interesting projects. Don't forget to say hi to Laurie, Eve en Aaron.

Beste Willem (paranimf), Simon en Jan: ach, gewoon simpel: zonder jullie hulp, interesse en betrokkenheid was een groot gedeelte van dit resultaat niet mogelijk geweest. Willem, heb je wel ooit nee tegen mij moeten verkopen? Ik kan het mij in ieder geval niet herinneren. Je fascinatie voor het menselijk lichaam en je respect voor de overledene zullen nog lang bij mij bewaard blijven. Je kennis over het menselijke lichaam laat me soms twijfelen of je niet stiekem een undercover anatoom bent. Maar nee, het ligt in jouw aard om dingen te doorgronden. Ik zal niet gauw onze gesprekken vergeten over de WOII, de bedevaart en je lange geschiedenis bij de pathologie en anatomie. En Simon, de stille kracht achter de anatomische wereld in Utrecht. Ik beloof je: we gaan een keer samen fietsen van Nieuwegein naar UMC Utrecht.

Geachte drs. Van Geffen en Bruhn, beste Geert-Jan en Jörgen: we hebben samen een deel van dit proefschrift tot stand gebracht. Jullie klinische toevoegingen op de stukken waren essentieel en maakten de artikelen kleurrijker, toegankelijker en bovenal gemakkelijker toepasbaar in de praktijk. Ik heb in jullie een gezonde dosis nieuwsgierigheid gezien die menig clinicus jaloers zou maken. En dat maakt dat jullie altijd met ideeën zitten waarvoor de tijd ontbreekt. Soms is dat best frustrerend, maar je kunt niet alles tegelijk hebben. Onze samenwerking zal nog lang voortduren en hopelijk zullen nog vele successen volgen.

Geachte dr. Bleys, beste Ronald, allereerst mijn grote dank dat je zo'n beetje de hele anatomie voor me ter beschikking hebt gesteld. Want zonder dat zou ik niet ver zijn gekomen. Je zeer kritische en analytische kijk op de stukken is bewonderenswaardig. Ik hoop dat de anatomie nog lang van je kwaliteiten en kunde kan profiteren.

Alle collega's op de afdeling Anesthesiologie en Anatomie, met name Toine Lim en Doetske The-Liem, Isabelle Theunissen, Matty Spinder, Jan-Willem de Groot, Jan Doorn en alle anderen, dank voor de verdieping en gezelligheid op de werkvloer. De koffiepauze rond half elf op Anatomie zou naar mijn idee verplicht opgenomen moeten worden in alle cao's.

Mijn dank gaat uit naar een aantal medische studenten die veel interesse en liefde voor het onderzoek heeft getoond; speciale eigenschappen die niet bij alle studenten te vinden zijn. Maartje Frijlink, Walid Moudrous (inmiddels al artsen) en Jantien Welleweerd hebben bergen werk verzet.

Externe financiers ben ik zeer erkentelijk voor de ondersteuning: Ministerie van Onderwijs, Cultuur en Wetenschap, vertegenwoordigd door de Nederlandse Organisatie voor Wetenschappelijk Onderzoek, NWO, in verband met de Mozaïek subsidie; de heer Aad van der El, oud rector van de SOMT. We hebben elkaar nooit ontmoet, maar zonder zijn primaire ondersteuning zou het digitale werk nooit tot stand zijn gekomen.

Esaote (dhr. van der Vlier en Stuit) heeft ultrasound-apparatuur beschikbaar gesteld en daarmee ook een deel van het onderzoek mogelijk gemaakt. Mijn hartelijke dank daarvoor.

Lieve pa en ma: zonder jullie was ik er niet geweest en zonder mij was dit proefschrift er niet geweest, dus zonder jullie geen proefschrift! Ik denk dat jullie meer genieten van dit moment dan wie dan ook...

Raid, Zafer, Ihsaan en Maryam (broers en zus): "eigenlijk" moeten we "gewoon" elkaar wat vaker zien. Wat voel ik me rijk met jullie. Hedil: bedankt voor je geduld.

Curriculum vitae

Nizar Moayeri werd op 28 april 1980 geboren in Al-Najaf Al-Ashraf, Irak en groeide achtereenvolgens op in Irak, Kuwait, Iran en Nederland. In 2000 behaalde hij zijn Atheneum diploma aan het Minkema college in Woerden. In 2001 behaalde hij zijn propedeuse Informatica aan de Universiteit Utrecht en in 2007 het arts-examen aan het UMC Utrecht. Tijdens het 100-jarig jubileum congres van de American Society of Anesthesiologists in 2005, won hij samen met zijn huidige co-promotor, de derde prijs van de Scientific and Educational Exhibit Award. In 2006 ontving hij een prestigieuze Fulbright beurs waarmee hij gedurende een half jaar in Pittsburgh, PA, onderzoek heeft gedaan naar de opbouw van het zenuwnetwerk in het nek- en schoudergebied, samen met dr. Paul Bigeleisen (University of Pittsburgh Medical Center) en dr. Gerbrand Groen (UMC Utrecht). Eind 2007 begon hij aan het promotieonderzoek onder begeleiding van dr. Gerbrand J Groen (promotor prof. dr. C.J. Kalkman) waaraan in augustus 2008 een NWO-Mozaïek beurs werd toegekend voor het gehele promotietraject.

Nizar Moayeri heeft in zowel nationale en internationale congressen actief geparticipeerd. Tevens heeft hij, samen met zijn co-promotor dr. Gerbrand Groen, gewerkt aan tot stand brengen van een omvangrijke atlas over *"Ultrasound in Regional Anesthesia & Pain Medicine"* onder redacteurschap van dr. Bigeleisen.

Na afronding van het promotietraject in september 2009 begon Nizar als arts-assistent op de afdeling Neurochirurgie van het UMC Utrecht, onder leiding van prof. dr. L. Regli.

List of publications

1. Moayeri N, Renes S, Van Geffen GJ, Groen GJ. Vertical infraclavicular brachial plexus block: needle redirection after elicitation of elbow flexion. *Reg Anesth Pain Med* 2009; 34: 236-41
2. Moayeri N, Groen GJ. Differences in quantitative architecture of sciatic nerve may explain differences in potential vulnerability to nerve injury, onset time, and minimum effective volume of local anesthetic. *Anesthesiology* 2009; 111: 1128-34
3. Moayeri N, Bleys RLAW, Welleweerd JC, Groen GJ. Diagnostic accuracy of ultrasound parameters to detect small volume intraneural injection in regional anesthesia. *submitted.*
4. Bruhn J, Moayeri N, Groen GJ, van Veenendaal A, Gielen MJ, Scheffer GJ, van Geffen GJ. Soft tissue landmark for ultrasound identification of the sciatic nerve in the infragluteal region: the tendon of the long head of the biceps femoris muscle. *Acta Anaesthesiol Scand.* 2009; 53: 921-25
5. Moayeri N, Moudrous W, Frijlink MS, Borgeat A, Groen GJ. Intraneural injection of local anesthetics and nerve injury. A systematic review. *submitted.*
6. Bigeleisen PE, Moayeri N, Groen GJ. Extraneural versus intraneural stimulation thresholds during ultrasound-guided supraclavicular block. *Anesthesiology* 2009; 110: 1235-43.
7. Van Geffen GJ, Moayeri N, Bruhn J, Scheffer GJ, Chan VW, Groen GJ. Correlation between ultrasound imaging, cross-sectional anatomy and histology of the brachial plexus: A review. *Reg Anesth Pain Med.* 2009; 34: 490-97.
8. Moayeri N, Van Geffen GJ, Bruhn J, Groen GJ. Ultrasound imaging, cross-sectional anatomy and histology of the sciatic nerve: A correlative review. *submitted.*
9. Moayeri N, Bigeleisen PE, Groen GJ. Quantitative architecture of the brachial plexus, surrounding compartments and their possible significance for plexus blocks. *Anesthesiology* 2008; 108: 299-304.
10. Bigeleisen PE, Moayeri N, Groen GJ. Ultrasound-guided supraclavicular block may be intraneural. *Anesthesiology, 2009 in press.*
11. Moayeri N, Bleys RLAW Bleys, Groen GJ. Diagnostic accuracy to detect intraneural injection in ultrasound-guided nerve blocks. *Anesthesiology* 2009 (abstract) A252.
12. Moayeri N, Groen GJ. Quantitative architecture of sciatic nerve may explain potential vulnerability to neural injury. *Anesthesiology* 2009 (abstract) A251.
13. Groen GJ, Moayeri N. Undisturbed anatomy in regional anesthesia: A new gold standard? *Anesthesiology* 2009 (abstract) A250.
14. Tan AY, Moayeri N, Hilmi IA, Planinsic RC, Meng L. Postoperative incidence and etiology of reintubation: A 4-Year Retrospective Analysis. *Anesthesiology* 2007 (abstract) A960.
15. Hilmi IA, Planinsic RC, Damian D, M.D., Sakai T, Moayeri N. Endotoxin levels as marker for liver graft performance in patients undergoing liver transplantation. *Anesthesiology* 2007 (abstract) A312.
16. Groen GJ, Moayeri N, Giezeman M, Bleys RLAW. Where to redirect the needle in the vertical infraclavicular block when electrical stimulation elicits shoulder abduction or elbow flexion? *Anesthesiology* 2005 (abstract) A1059.
17. Groen GJ, Moayeri N. Interactive regional anesthesia resident training by real-time anatomy imaging. *Anesthesiology* 2005 (abstract) A967.