Cross-sectional area reference values for peripheral nerve ultrasound in adults: A systematic review and meta-analysis—Part III: Cervical nerve roots and vagal nerve

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Abstract

Background and purpose: Measurement of the cross-sectional area (CSA) of cervical nerve roots using ultrasound is useful in the evaluation of inflammatory polyneuropathies, and measurement of CSA of the vagal nerve might give information about involvement of the autonomic nervous system. We performed a systematic review and meta-analysis of published CSA reference values for cervical nerve roots and vagal nerve.

Methods: We included available-to-date nerve ultrasound studies on healthy adults and provide meta-analysis for CSA of the following nerves: cervical nerve roots C5, C6, and C7 as well as vagal nerve in the carotid sheath at the carotid bifurcation level. We report regression and correlation analyses for age, gender, height, weight, and geographic continent.

Results: We included 11 studies with 885 healthy volunteers (mean age = 42.7 years) and 3149 examined nerve sites. Calculated mean pooled CSA of C5 root was 5.6 mm² (95% confidence interval [CI] = 4.6–6.7 mm², n = 911), of C6 root was 8.8 mm² (95% CI = 7.4–10.3 mm², n = 909), of C7 root was 9.5 mm² (95% CI = 8.0–10.9 mm², n = 909), and of vagal nerve was 2.2 mm² (95% CI = 1.5–2.9 mm², n = 420). No heterogeneity was found across studies for any site. Subgroup analysis revealed no significant effects of age, gender, height, weight, and geographic continent on CSA for any of these nerve sites.

Conclusions: We provide the first meta-analysis on CSA reference values for the cervical nerve roots and the vagal nerve, with no heterogeneity of reported CSA values at all nerve sites. Our data facilitate the goal of an international standardized evaluation protocol.

Keywords
C5, C6, C7, cervical nerve roots, nerve ultrasound, sonography, vagal nerve
INTRODUCTION

Imaging of the cervical nerve roots and the vagal nerve using ultrasound has been increasingly described in recent years. Enlargement of the cross-sectional area (CSA) of cervical nerve roots was described in radiculopathy [1,2] as well as in inflammatory polyneuropathies such as chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy [3,4]. CSA of the vagal nerve might give information about involvement of the autonomic nervous system [5], and a reduction in comparison to healthy individuals was described in Parkinson disease [6]. Due to the increasing use of nerve ultrasound, several study groups published reference values for CSA measured by tracing nerve boundaries for a number of anatomic sites [7–10]. However, reported reference values show a great variability of measured CSA [7,11]. Some authors reported effects of age, weight, and gender on CSA [8,12], whereas others could not confirm any association [13]. Therefore, we performed a meta-analysis on CSA reference values of peripheral nerves measured by nerve ultrasound. In this third part of our analysis, we report the results referring to the cervical nerve roots C5–C7 and the vagal nerve. We performed a systematic review and meta-analysis of published CSA reference values for cervical nerve roots and vagal nerve.

METHODS

This meta-analysis is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline [14]. A systematic literature search of the MEDLINE and Scopus databases was performed by two independent reviewers (A.L.F. and K.P.). The following search terms were used for database search: Nerve AND (sonography OR ultrasound) AND (normal values OR reference values). All studies found before February 2020 were independently reviewed by A.L.F. and K.P. The title and abstract of the studies were screened for whether the studies matched the content of this meta-analysis. Only studies measuring CSA of peripheral nerves with B-mode sonography in healthy adult subjects were included. The following nerves were analyzed: median nerve at wrist, forearm, and upper arm; ulnar nerve at Guyon loge, forearm, elbow, and upper arm; radial nerve at upper arm; nerve roots C5, C6, and C7; vagal nerve in the carotid sheath at the level of carotid bifurcation; fibular nerve at fibular head and popliteal fossa; tibial nerve at popliteal fossa and malleolus; and sural nerve at the level of the two heads of gastrocnemius muscle.

Information from the abstract and main text of the identified studies was extracted on characteristics of study participants (including mean age, sex, height, weight, year, and country in which the study was performed), methodology (ultrasound device, transducer frequency, measurement sites), and mean CSA of peripheral nerves (including SD).

This procedure was performed separately by two investigators (A.L.F. and K.P.). Disagreements were resolved by discussion between the two review authors and the senior author (C.K.).

The study protocol was not registered in any database.

Statistical analyses

Pooled analyses of mean CSA in both the overall and subgroup analyses were calculated with the random effects model (DerSimonian–Laird model). Multivariate meta-regression analyses of CSA measurements with age, height, weight, and male prevalence were also performed under the random-effects model. The equivalent z-test was performed for each pooled estimate, and if \( p < 0.05 \), it was considered statistically significant. We assessed heterogeneity among studies with the Cochran Q and \( I^2 \) statistics. For geographic subgroup analyses, we used a standard test for heterogeneity across subgroup results to investigate for potential differences between subgroups. All analyses were conducted in STATA/MP 16.0 (StataCorp) with the metan and metareg packages. Data are available from the authors upon request.

RESULTS

Included studies

We found 1333 potentially relevant studies, from which 125 eligible studies were retained for full-text evaluation after screening titles and abstracts. A total of 114 studies were excluded after consensus of the two reviewers, most of them due to missing information about SD or due to missing data for cervical nerve roots and vagal nerve (Table S1. Appendix S1). Eleven studies were included in the review and meta-analysis (Table S2. Appendix S1, Figure 1). Five studies were conducted in Europe, four in Asia, and two in the United States. The range of frequencies used as ultrasound probe was between 5 and 18 MHz. A total of 3149 measurements of cervical nerve root and vagal nerve of cumulatively 885 healthy people were analyzed. All studies included healthy adults older than 18 years. Mean age was 42.7 years. Mean proportion of female patients was 54%.

CSA reference values and heterogeneity of reported values

Calculated mean pooled CSA of C5 root was 5.6 mm\(^2\) (95% confidence interval [CI] = 4.6–6.7 mm\(^2\), \( n = 911 \)). Calculated mean pooled CSA of C6 root was 8.8 mm\(^2\) (95% CI = 7.4–10.3 mm\(^2\), \( n = 909 \)). Calculated mean pooled CSA of C7 root was 9.5 mm\(^2\) (95% CI = 8.0–10.9 mm\(^2\), \( n = 909 \)).
Calculated mean pooled CSA of vagal nerve in the carotid sheath at the level of carotid bifurcation was 2.2 mm² (95% CI = 1.5–2.9 mm², n = 420).

No heterogeneity was found across studies for any site. These results are shown in Table 1. Figures 2–5 show the results of the meta-analysis of CSA for each cervical root and the vagal nerve.
Correlations of CSA with age, gender, height, weight, and geographic differences

No significant effects of age, gender, height, weight, and geographic continent could be found in univariate or multivariate regression analysis for any of these sites.

DISCUSSION

For the first time, results of a meta-analysis of ultrasound CSA reference values for cervical nerve roots and vagal nerve are presented in this study.

CSA values depicted in this meta-analysis show that the size of the cervical nerve roots increases from C5 to C7, which is in line with the anatomical literature [15]. Nerve roots may be difficult to examine in patients with a short neck or obesity, whereas imaging of vagal nerve in the carotid sheath is comparatively easy. Despite this, we found no heterogeneity either for the CSA of the cervical nerve roots or for the CSA of the vagal nerve. Clear anatomical landmarks for identifying the cervical nerve roots were defined and described in detail and consistently by most authors. Takeuchi et al. define the measuring site “at the point where the nerve root appeared between the anterior and posterior tubercle of the transverse process” [16]. Haun et al. define it “at the most proximal location possible, usually at the point where the nerve root exited over the transverse process or just distal to that point” [17], and state that recognition of the level of the C7 vertebra is possible due to the absence of the anterior tubercle from its transverse processes, in contrast to the other cervical nerve roots, where both anterior and posterior tubercles exist [18]. This exact description probably led to excellent results regarding heterogeneity despite possible difficulties in imaging.
This supports the use of ultrasound of cervical nerve roots and vagal nerve by well-trained examiners.

For vagal nerve, Walter and Tsiberidou showed that different measurement techniques can produce different results [19]. However, the level of examination of the vagal nerve was also well defined and similar in the studies described in this meta-analysis (carotid bifurcation level), resulting in low heterogenicity. Only one study described the examination level of vagal nerve in relation to thyroid gland and not in relation to carotid bifurcation [20].

In this meta-analysis, no correlation of CSA of cervical nerve roots and vagal nerve with age, height, weight, gender, or geographic region was found, suggesting that the influence of age, height, and weight do not need to be considered in everyday clinical practice. However, there are only a few studies reporting on ultrasound of cervical nerve roots and vagal nerve; therefore, a low number of available studies could be the reason for missing correlations. For other peripheral nerves, slight correlations of CSA with height, weight, body mass index (BMI), gender, and age were described in some observational studies [8,12] and part I and II of our meta-analysis [21]. Anatomical reasons could be an explanation for the missing correlation of demographics with vagal nerve and cervical nerve roots, for example there could be less correlation with height and BMI, the more proximal a nerve site.

Overall, polyneuropathy ultrasound protocols using the anatomical regions described in this meta-analysis have been established in recent years. We hereby provide meta-analytical data for these regions and, therefore, recommend using these examination sites to reach an internationally standardized paraclinical evaluation. Nonetheless, each ultrasound laboratory should compare its own normal values to the results of this meta-analysis and aim to reduce deviations as much as possible. Internationally standardized protocols are necessary to avoid methodological differences.

One limitation for the meta-analysis is that we did not regard size differences of left and right vagal nerve due to missing information on

**FIGURE 3** Meta-analysis of cross-sectional area (CSA) of C6 root in healthy controls. Mean CSA and 95% confidence interval (CI) are shown in millimeters. Studies are sorted by geographic region: 1, Europe; 2, United States; 3, Asia
body side in some articles. A morphological asymmetry between both vagal nerves was described before [5], with the right one being larger than the left. A reason may be that the right vagal nerve predominantly innervates parts of the small intestine and the colon, whereas the left one innervates the stomach, the liver, and the superior part of the duodenum [22]. Also, cardiovagal innervation was described as asymmetric [5]. We did not regard these side differences in our current analysis.

Another limitation is that the associations detected at the population level might not be present at the individual patient level (ecological fallacy). Beyond this, we could not analyze the influence of ultrasound device or frequency of ultrasound probe on CSA values, as various devices were used, and frequencies were only given as a range (i.e., 8–15 MHz) in the majority of publications. Moreover, in very few publications were different anatomical regions examined, for example, the brachial plexus in the interscalene or supraclavicular space; these were not included in this analysis.

In this third part of our meta-analysis, we report only on results for cervical nerve roots and vagal nerve. Much more studies report on ultrasound of peripheral nerves of the extremities, which we relate to in Parts I and II of our meta-analysis.

Concluding, for the first time, we provide reference values for CSA of cervical nerve roots and vagal nerve that are based on meta-analysis of 4149 examined nerve sites. No heterogeneity was found for CSA reported for any of these sites. Subgroup analysis revealed no influence of age, gender, region, height, and weight. Our meta-analytical data facilitate the goal of an international standardized evaluation protocol.

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CONFLICT OF INTEREST
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AUTHOR CONTRIBUTIONS
Anna Lena Fisse: conceptualization (equal), data curation (equal), formal analysis (supporting), investigation (lead), methodology (supporting), project administration (lead), resources (equal), supervision (equal), validation (supporting), writing—original draft (supporting), writing—review & editing (equal). Aristeidis H. Katsanos: conceptualization (equal), data curation (supporting), formal analysis (lead), methodology (lead), project administration (supporting), resources (supporting), software (lead), supervision (equal), validation (equal), visualization (lead), writing—original draft (supporting), writing—review & editing (equal).

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Kalliopi Pitarokoili: conceptualization (equal), methodology (supporting), project administration (equal), supervision (equal), validation (supporting), writing—original draft (supporting), writing—review & editing (equal). Ralf Gold: conceptualization (supporting), funding acquisition (lead), project administration (supporting), resources (lead), supervision (supporting), writing—review & editing (supporting). Christos Krogias: conceptualization (equal), data curation (supporting), formal analysis (lead), methodology (lead), project administration (supporting), resources (supporting), software (lead), supervision (equal), validation (equal), visualization (lead), writing—original draft (supporting), writing—review & editing (equal).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.