Intraneural Vascular Resistive Index of the Median Nerve as a Predictor of Severity of Carpal Tunnel Syndrome

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ABSTRACT
Objective: There is a limited data about resistive index (RI) of median nerve (MN) in patients with carpal tunnel syndrome (CTS). In our study, we aimed to evaluate the relationship between CTS severity and MN-RI.
Methods: A total of 115 CTS patient wrists, and 49 wrists of control subjects without CTS, were examined on ultrasonography (US) and color Doppler US (CDUS), pulsed Doppler ultrasonography (PDUS), and by electrophysiological evaluations. MN peak-systolic velocity (MN-PSV), MN end-diastolic velocity, MN-RI and MN pulsatility index (MN-PI) were measured by PDUS. Patients were divided into 3 groups according to electrophysiological examinations severity findings of CTS as mild (Group-I), moderate (Group-II), and severe (Group-III).
Results: MN-PSV, MN-PI and MN-RI increased significantly from Group-I to Group-III and these parameters were significantly higher in Group-III than other two groups. MN-RI independently determines the patients to have severe CTS. Increased MN-RI (per-0.1) was found to increase the risk of having severe CTS by 3.45-times. In the ROC analysis, the area under the curve was 0.846 for MN-RI. When the MN-RI cut-off value was taken as 0.80, it determines patients to be severe CTS with 85.2% sensitivity and 78.2% specificity.
Conclusion: The increase in MN-RI in CTS patients is independently associated with disease severity and may be used in the clinical follow-up of these patients.
Keywords: Carpal tunnel syndrome, median nerve, pulsed doppler ultrasoundography, resistive index

INTRODUCTION
Carpal tunnel syndrome (CTS) is the most predominant entrapment neuropathy of the median nerve (MN) constricted in the wrist. It is more common in middle-aged women (1). CTS affects 1% of the general population, and the prevalence is 5.8% for females and 0.6% for males (2). The MN is located tightly packed in the carpal tunnel (CT) with 9 tendons and synovial membranes. CTS may occur idiopathically, as well as in rheumatoid arthritis, hyperthyroidism, acromegaly, and diabetes mellitus (3). Pathologic changes occur in CTS due to MN pressure (4). Anatomic variations such as bifid median nerve anomaly and persistent median artery synovitis and cyst, ganglion, aberrant muscle, a tumor that may cause nerve compression in the CT can be detected by imaging methods (5). Ultrasonography (US) is the most commonly used imaging technique for this purpose. The fact that patients are not exposed to X-rays or contrasts, being a cheap, well-tolerated, noninvasive, ready-for-intervention, easily accessible, and easy-to-implement process, are the significant advantages of US.

In addition to anatomical parameters, MN epineural and intra-neural blood flow can be revealed by Doppler US (6). These Doppler US are color Doppler US (CDUS), pulsed Doppler ultrasonography (PDUS), and by electrophysiological evaluations. MN peak-systolic velocity (MN-PSV), MN end-diastolic velocity, MN-RI and MN pulsatility index (MN-PI) were measured by PDUS. Patients were divided into 3 groups according to electrophysiological examinations severity findings of CTS as mild (Group-I), moderate (Group-II), and severe (Group-III).

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Conclusion: The increase in MN-RI in CTS patients is independently associated with disease severity and may be used in the clinical follow-up of these patients.

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systolic velocity (PSV) can be revealed (7-13). There are studies that investigate CTS severity with intraneural PSV (1, 8). There is limited information about the change of MN resistive index (RI) and its clinical significance in CTS patients (14).

Magnetic resonance imaging (MRI) and US are two important techniques for the diagnosis and severity assessment of CTS. MN CSA diffusion tensor imaging (DTI) findings obtained from different levels with MRI have been shown to be closely associated with CTS severity (15, 16). In a study by Ikeda et al. (15), the CSA in the affected hand at the scaphoid body level was significantly larger rather than that in the unaffected hand. The CSA at the scaphoid body level positively correlated with distal motor latency in the affected hand. In a study by Wang et al. (16), the fractional anisotropy and apparent diffusion coefficient values obtained by DTI were reported to be closely associated with the diagnosis and severity of CTS. However, MRI for CTS evaluation is more expensive and difficult to reach than US examination. It was shown that MN CSA, MN vascularity increase, and MN-PSV and SMI were significant in order to determine the diagnosis and severity of CTS obtained by B-mode, CDUS, and PDUS (6, 7, 10, 11). However, other studies have reported no clear association between these findings and CTS severity (7, 12, 13). US is easily accessible, cheaper than the MRI, but is still not recommended as an objective and clear parameter. In most studies, MN vascularity has been shown to increase in CTS patients.

It has been shown that RI obtained from the renal artery, hepatic artery, splenic artery, and carotid artery determines the damage to the endothelium in these organs or related diseases (17-20). We think that MN compression, that occurs in patients with CTS, may also increase the RI and associated PDUS parameters in the arteries within this nerve by pressurizing the vasculature. There is limited information about the clinical use of the MN-RI value obtained by PDUS in CTS patients (14). In only one study, MN-RI values obtained by PDUS were reported to be significantly higher in patients with MN involvement than in those without MN involvement. However, this study did not give us any information on the relationship between the MN-RI value and the severity of CTS disease (14).

In this study, we aimed to investigate the relationship between PDUS findings of MN and CTS severity in patients diagnosed CTS with clinical and electrophysiological examinations.

**METHODS**

**Patients and Study Design**

One hundred and fifteen wrists of 82 patients (12 males, 70 females, mean age 51.9±10.9 years) with CTS, who were referred to our physical medicine and rehabilitation outpatient clinic between April 2014 and April 2015, were evaluated on US, CDUS, and PDUS. CTS diagnosis was confirmed by both clinical and electrophysiological examinations. All patients had signs of paraesthesia, pain, and/or vasomotor symptoms of MN injury. For clinical assessment, provocative tests, including Allen’s test, Tinel test, and carpal compression test, were used. Patients with at least one positive provocative test were given preliminarily diagnosed with CTS. Electrophysiological examinations were performed using a four-channel Medelec Synergy (Oxford Instruments Medical, Surrey, UK) electromyography device. Neurophysiological tests included nerve conduction studies and needle electromyography for the median and ulnar nerves. Nerve conduction studies included measurement of the distal sensory and distal motor latencies and sensory/motor nerve conduction velocities. The exact diagnosis of CTS was made according to the most recently updated guidelines (21). CTS severity was classified, on the basis of electrophysiological results, as mild, moderate, severe, or extreme, according to the modified scoring system of Padua et al. (22). Patients were excluded if they had polynuropathy, radiculopathy, brachial plexus injury, proximal median neuropathy, diabetes mellitus, hypothyroidism, rheumatoid arthritis, amyloidosis, chronic renal failure managed by hemodialysis, pregnancy, and a history of surgery for CTS.

Forty-nine clinically and electrophysiologically normal wrists were included in the control group.

CDUS and electrophysiological evaluations were performed in all controls.

The study protocol was prepared according to the principles of the Declaration of Helsinki. The ethics committee of Baskent University Faculty of Medicine approved the study protocol, and each participant provided written informed consent.

**Median Nerve Ultrasonography**

All subjects were examined on B-mode and CDUS using a 13-MHz linear array transducer (Sonoline Antares; Siemens Medical Solutions, Inc., Hoffman Estates, IL, USA) in the neutral supine position. All examinations were performed by a single radiologist who had 15 years of work experience. The MN from the distal forearm to the carpal tunnel outlet was assessed in the transverse and longitudinal planes. Three internal anatomic landmarks were used for the images. The images of the MN were obtained at the radial-ulnar junction immediately proximal to the flexor retinaculum, and at the level of the pisiform and the hook of the hamate (23, 24). MN vascularity was evaluated with CDUS, and flow velocity measurements were analyzed with PDUS. Repeated measurements and at least 8 waveforms of intraneurual arteries were obtained. PSV, end-diastolic velocity (EDV), pulsatility index (PI), and RI of intraneural arteries were measured on PDUS (Figure 1). MN-RI and MN-PI values were measured automatically by PSV-EDV/PSV formula, and PSV-EDV/MV (mean flow velocity) formula, respectively. The mean values of MN-PSV, MN-EDV, MN-PI, and MN-RI were recorded (Figure 1a-d).

**Statistical Analysis**

Continuous variables were expressed as mean±standard deviation (mean±SD), while categorical variables were reported as...
counts and percentages. Comparisons of continuous variables were performed by the One-way ANOVA or Kruskal-Wallis 1-way ANOVA tests according to the distribution. For normally distributed data, the Scheffe and Games-Howell tests were used for multiple comparisons of groups with respect to the homogeneity of variances. For non-normally-distributed data, the Bonferroni-adjusted Mann Whitney U test was used for multiple comparisons of groups. The Chi-Square Test was used to compare categorical variables. Univariate analysis revealed demographic and Doppler US parameters that were significantly different in patients with CTS severity. For independent determination of patients who had severe disease for CTS, multivariate logistic regression analysis was performed. ROC curve analysis was performed to reassess markers that were independent for identifying patients with severe disease for CTS and to determine the threshold values of these markers. The value of the area under the curve was used as the accuracy criterion of the test. The threshold for statistical significance was set at p<0.05. All analyses were performed with SPSS 20.0 (IBM SPSS Corp.; Armonk, NY, USA) statistical software package.

RESULTS
The median MN-PSV, MN-EDV, MN-PI, and MN-RI values were 5.3 cm/s, 1.2 cm/s, 2.0 cm/s, and 0.79 cm/s, respectively. The median values of the same parameters in patients with severe CTS were 7.2 cm/s, 1.1 cm/s, 2.71 cm/s, and 0.88 cm/s, respectively. The demographic findings and PDUS scores of the patients were evaluated according to the previously-mentioned CTS groups. In the control group, no hypervascularization was detected in any of the subjects.

Demographic and Ultrasonography Findings of the Study Groups
There was no significant difference between groups in terms of demographic (age and gender) parameters. MN-PSV, MN-PI,
and MN-RI increased significantly from Group I to Group III, and these parameters were significantly higher in Group III than in the other two groups (Table 1, Figure 2a-d). Also, MN-PSV, MN-PI, and MN-RI were higher in Group II than in Group I, though the difference was not statistically significant (Table 1). MN-EDV was similar among the groups (Table 2, Figure 2b).

**Multivariate Logistic Regression Analysis for the Detection of Patients with Severe CTS**

Multivariate logistic regression analysis was performed to determine the closest relationship between CTS severity and age, gender, MN-PSV, MN-EDV, MN-RI, and MN-PI. Upon multivariate logistic regression analysis, it was found that only MN-RI independently identified the patients with severe CTS (Odds Ratio=3.449, 95% Confidence Interval: 1.147–8.392, p<0.001; Table 2). According to this analysis, increased MN-RI (per 0.1) was found to increase the risk of patients having severe CTS by 3.45 fold (Table 2).

**ROC Analysis for the Detection of Patients with Severe CTS**

In the ROC analysis, the area under the curve was 0.846 for MN-RI for the prediction of severe CTS group (Area Under Receiver Operating Characteristic Curve=0.846, 95% Confidence Interval=0.762–0.930, p<0.001, p<0.05, Table 3 and Figure 3). An MN-RI value of 0.80 determined identified severe CTS with 85.2% sensitivity and 78.2% specificity.

**DISCUSSION**

The main finding in this study is that increased MN-RI obtained by PDUS independently predicts the severity of CTS patients. To our knowledge, this is the first study in the literature that inspects this relation. When the MN-RI cut-off value is taken as >0.80, it determines the risk of severe CTS development with acceptable sensitivity and specificity.

Electromyography is recommended as the gold standard with electrophysiological examinations in the evaluation of patients.
with CTS in daily practice and in determining disease severity (6). However, with electromyography, just electrophysiological properties of MN are shown. The MN entrapment status is shown indirectly. In addition, electromyography has electrode and needle placement problems (25). As a matter of fact, in order to complete these disadvantages and its deficiencies, MN US examination was recommended in the evaluation of CTS patients in 1990 guidelines (26). US examination was initially proposed as an adjunctive one rather than a diagnostic one and used as an adjunctive modality for detecting nerve abnormalities (such as bifid MN), and mass lesions, or guiding injection treatments. The B-mode US of MN provides information about the nerve anatomy and also can detect the transverse carpal tunnel ligament pressure (5, 25). MN CSA is also calculated with B-mode US, and the CSA increase is reported to be associated with the presence of CTS and CTS severity (6, 27). However, in some studies, CSA and CTS severity are not related (7, 12, 13). In the CTS guidelines, MN CSA has been recommended as a new study on this issue because of the lack of the precise location of the measurement site and having a very good cut-off value (21), because there are too many publications that have different threshold values (21).

Many studies have been carried out with the view that this increased vascularity is associated with direct nerve pressure may be associated with disease severity. Initially, CDUS was used, and in a large majority of these studies, MN vascularity was shown to be increased in CTS patients (6, 11, 28, 29) and reported to be important for diagnosis. However, the question as to whether increased vascularity is associated with disease severity is unclear and has conflicting results. In some of these studies, the severity of CTS was associated with increased MN vascularity (10, 11), although some studies did not correlate with CTS severity (12, 25, 26, 30). At the same time, the increase in vascularity is a relative and subjective measurement, resulting in a preference for flow velocity and pattern obtained with PDUS. The last published guideline also recommended more objective studies of vascularity enhancement (21). With the recent MN-PSV study (1, 8), there is currently limited MN-RI examination as far as we have investigated, and our study is second in the literature (14). A similar study was performed

| Table 1. Demographic and Doppler ultrasonography findings of the study groups |
|------------------|------------------|------------------|------------------|------------------|
| Variable         | Group I n=36     | Group II n=52    | Group III n=27   | p                |
| Age (year)       | 50.1±11.4        | 53.1±9.9         | 51.9±11.9        | 0.469            |
| Gender (male/female) | 5/31            | 9/43             | 6/21             | 0.692            |
| Median nerve peak systolic velocity (cm/s) | 4.63±2.94       | 5.43±2.26        | 8.94±2.26        | <0.001           |
| Median nerve end diastolic velocity (cm/s)  | 1.50±0.82       | 1.55±1.34        | 1.22±0.69        | 0.407            |
| Median nerve pulsatility index          | 1.80±1.19       | 1.84±0.82        | 3.02±1.15        | <0.001           |
| Median nerve resistive index          | 0.61±0.23       | 0.71±0.17        | 0.85±0.76        | <0.001           |

The values were shown as mean±standard deviation or n (%), Group I=Control group, Group II=Medical treatment group and Group III=Planned surgery group

| Variable         | ODds Ratio | 95% Confidence Interval | p       |
|------------------|------------|-------------------------|---------|
| Age (year)       | 0.965      | 0.907–1.026              | 0.257   |
| Gender (male/female) | 0.588    | 0.113–3.052              | 0.528   |
| Median nerve peak systolic velocity (cm/s) | 1.194     | 0.972–1.466              | 0.091   |
| Median nerve end diastolic velocity (cm/s)  | 0.325     | 0.039–2.728              | 0.300   |
| Median nerve pulsatility index          | 0.927     | 0.372–2.310              | 0.870   |
| Median nerve resistive index          | 3.449     | 1.147–8.392              | <0.001  |

| Variable         | Area Under Receiver Operating Characteristic Curve | p       | Cut-off value | Sensitivity | Specificity |
|------------------|--------------------------------------------------|---------|--------------|-------------|-------------|
| Median nerve resistive index | 0.846 (0.762–0.930) | <0.001 | 0.80         | 85.2%       | 78.2%       |

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MN-RI value and its importance in patients with severe CTS is accepted in many studies. A new review of MN vascularity was not evaluated in our study. Better and more meaningful results could be obtained if we had assessed the SMI in our study. In conclusion, PDUS findings may contribute to the diagnosis of severe carpal tunnel syndrome.
CONCLUSION
According to our results, the increase in the MN-RI in CTS patients is independently associated with disease severity and may be used in the clinical follow-up of these patients. We think that MN-RI evaluation should be a part of the assessment of CTS. Clinicians should consider patients with MN-RI >0.80, as serious CTS.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Başkent University School of Medicine (24.06.2015/ KA15/204).

Informed Consent: Written informed consent was obtained from participants who participated in this study.

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