A Sonographic Quantitative Cutoff Value of Cerebral Venous Outflow in Neurologic Diseases: A Blinded Study of 115 Subjects

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ABSTRACT

BACKGROUND AND PURPOSE: The autonomic nervous system maintains constant cerebral venous blood outflow in changing positions. Alterations in cerebral autoregulation can be revealed by postural changes at quantitative color Doppler sonography. The aim of this study was to reach an optimal cutoff value of the difference between the cerebral venous blood outflow in the supine and seated positions that can discriminate healthy controls from patients with multiple sclerosis and those with other neurologic diseases and to evaluate its specificity, sensitivity, and diagnostic accuracy.

MATERIALS AND METHODS: One hundred fifteen subjects (54 with MS, 31 healthy controls, 30 with other neurologic diseases) underwent a blinded quantitative color Doppler sonography evaluation of cerebral venous blood outflow in the supine and sitting positions. An optimal difference value between the supine and sitting positions of the cerebral venous blood outflow cutoff value was sought.

RESULTS: The difference value between supine and sitting positions of the cerebral venous blood outflow was $\Delta$503.24 in 38/54 (70.37%) patients with MS, 9/31 (29.03%) healthy controls, and 13/30 (43.33%) subjects with other neurological diseases. A difference value between supine and sitting positions of the cerebral venous blood outflow at a 503.24 cutoff reached a sensitivity at 70.37%, a 70.96% specificity, a 80.85% positive predictive value, and a 57.89% negative predictive value; the quantitative color Doppler sonography parameters yielded significant differences. The difference value between supine and sitting positions of cerebral venous blood outflow $\leq$ 503.24 assessed the significant difference between MS versus other neurological diseases.

CONCLUSIONS: Alteration of cerebral venous blood outflow discriminated MS versus other neurologic diseases and MS versus healthy controls. The difference value between supine and sitting positions of cerebral venous blood outflow $\leq$ 503.24 was statistically associated with MS.

ABBREVIATIONS: AUC = area under the curve; CVF = cerebral venous blood outflow; $\Delta$CVF = difference value between supine and sitting positions of the cerebral venous blood outflow; HC = healthy controls; OND = other neurologic diseases

Complete evaluation of the cerebral venous circulation is difficult due to its anatomic variability. In vivo study of this system began in the 1970s by venography. Venography is still considered the criterion standard; however, only color Doppler sonography can evaluate dynamic aspects, including the efficiency of the jugular valves or flow characteristics in sitting and supine positions. MR venography can be a noninvasive imaging technique for the morphologic detection of extracranial venous anomalies in the internal jugular and vertebral veins in patients with multiple sclerosis, but it cannot give a dynamic evaluation. Phase-contrast MR imaging was used to measure venous flow in the internal jugular and epidural veins but only in the supine position. MR perfusion demonstrates a hypoperfusion of white and gray matter, and the parameters involved are cerebral blood volume, cerebral blood flow, and mean transit time, but not cerebral venous blood outflow (CVF).

Disorders involving the cerebral venous system may result in CVF insufficiency, elevation of venous pressure, and an increase of intracranial pressure and may lead to parenchymal abnormalities. Compliance of the venous system depends on anatomic variants and the onset timing of venous pathologies. Multiple sclerosis is defined as an inflammatory demyelinating disease of the CNS, with presumed autoimmune etiology, which occurs in ge-
The aim of the present study was to identify the cutoff value of ΔCVF that maximizes the diagnostic accuracy of the model. Its specificity, sensitivity, and diagnostic accuracy in 3 different groups of patients, those with MS, those with other neurologic diseases (OND), and healthy controls, were evaluated.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of our institution, and written informed consent was obtained from all subjects.
**Statistical Analysis**

The reliability of the results obtained by 2 operators was calculated by using the Fleiss $\kappa$ index. The frequency distributions of the $\Delta$CVF cutoff value among the subjects in the MS, HC, and OND groups were displayed as contingency tables. The differences between the proportions of the outcomes of this diagnostic index over the MS, HC, and OND groups were assessed through the Marascuilo procedure, which enabled simultaneous testing of the differences of all pairs of proportions. The Kruskal-Wallis test was applied to compare the distributions of the $\Delta$CVF cutoff value among the groups and to evaluate the differences among the sub-classes of MS disease. In either case, the post hoc tests were performed by the Dunn multiple comparison test.

All the statistical tests were 2-tailed, and the significance level was fixed at .05.

The errors of classification were reported in terms of sensitivity, specificity, negative predictive value, and positive predictive value (PPV), along with their 95% confidence intervals. The odds ratio was also provided, and its $P$ value was determined by the Fisher exact test. The capability of the $\Delta$CVF cutoff value to classify the MS forms (relapsing-versus-progressive) was reported as ORs.

The cutoff (ie, the threshold of the $\Delta$CVF) had been initially set to zero—namely the negative values of $\Delta$CVF were considered prognostic of pathologic status or “events,” while the positive values of $\Delta$CVF, as predictive “nonevents.” By increasing the level of the threshold, we expected to decrease the number of the false-negative predicted cases because 68.52% of the patients with MS had a positive $\Delta$CVF.

Performances of the models were assessed by the receiver operating characteristic analysis curve, which is reported to be the most opportune approach and a comprehensive description and measurement of diagnostic accuracy because it estimates all of the combinations of sensitivity and specificity that a diagnostic test can produce.24,25 The range of the cutoff values from which selecting the optimal threshold was formed by the percentiles of the distribution of the $\Delta$CVF in the HC group not only because the healthy condition is usually adopted as the reference standard in a diagnostic test, but also because the $\Delta$CVF distributions of HC and OND groups were largely overlapping. Every percentile was, in turn, set as the “potential best threshold” (this implies, from time to time, establishing, a priori, the specificity of the test). Then, in correspondence with each percentile, the number of subjects (from MS, HC, OND) with a $\Delta$CVF lower than the potential cutoff was counted as an “event” (ie, abnormal—this means, from time to time, determining the sensitivity of the test). Hence, by varying the percentile, it has been possible to trace the relationship between sensitivity and specificity to give rise to the receiver operating characteristic analysis curve.

The optimal positive cutoff threshold was determined in correspondence to the best compromise among sensitivity, specificity, and PPV.

We measured the area under the receiver operating characteristic analysis curve (AUC); and its statistical significance against the null hypothesis of $AUC = 0.5$ was assessed by means of the $Z$-test.26 The area under the curve can take values between 0.5 and 1.0. The greater the area under the curve (ie, the more the curve approaches the vertex of the graph), the greater the discriminating power of the test will be. For the interpretation of the values of the area below the receiver operating characteristic analysis curve, we referred to the classification proposed by Swets:27 $AUC = 0.5$, the test is not informative; $0.5 < AUC \leq 0.7$, the test is slightly accurate; $0.7 < AUC \leq 0.9$, the test is fairly accurate; $0.9 < AUC < 1.0$, the test is highly accurate; and $AUC = 1$ is a perfect test.

The robustness of the $\Delta$CVF model was tested by using an independent (“test”) sample made of 52 subjects with MS and 27 HC. Thus, the AUC of the test set was evaluated, and in correspondence to the best threshold estimated from the “training” set (ie, the given sample), we traced the values of sensitivity, specificity, and accuracy for the test set.

An internal test set (ie, a cross-validation test) is used for getting an independent OND sample by iterating the leave-$n$-out algorithm 2000 times. A different subset of the data (10 records) was held out each time, so that the training sets included 20 subjects and the out-of-sample, 10 subjects. The medians of the classification errors obtained from each partition were calculated; then, the sensitivity, specificity, and diagnostic accuracy were assessed. Last, the AUCs measured from the training and testing samples were compared.

Logistic regression was applied to predict the realization of the variable $\Delta$CVF dichotomized (according to the cutoff value), as a function of the demographic and clinical regressors—namely, age, sex and Expanded Disability Status Scale.

**RESULTS**

The Fleiss $\kappa$ index, calculated on 30 subjects (10 with MS, 10 HC, 10 with OND), was 0.9333, and its confidence interval (95%) was 0.8402–1.0264. Therefore, the observed agreement between the 2 operators was not accidental ($z = 5.1117$, $P < .0001$).

An optimal cutoff value of the $\Delta$CVF was reached at the 30th percentile (ie, $\Delta$CVF = 503.24) of the HC data distribution. $\Delta$CVF < 503.24 was present in 38/54 (70.37%) patients with MS, 9/31 (29.03%) HC, and 13/30 (43.33%) subjects with OND. The null hypothesis of equal proportions was rejected ($\chi^2 = 14.7584$, $P = .0006$, power = 0.9405).

By comparing MS versus HC groups with a cutoff of $\Delta$CVF = 503.24, the sensitivity was 70.37%; the specificity, 70.97%; the PPV, 80.85%; and the negative predictive value, 57.89%; the OR calculated for $\Delta$CVF < 503.24 was significant (5.81, $P = .00016$). Given OND versus HC, the sensitivity was 45%; the specificity, 70.97%; the PPV, 50%; the negative predictive value, 66.67%; and the OR was not significant (OR = 2, $P = .1091$). If one compared MS and OND, the sensitivity was 70.37%; the specificity, 55%; the PPV, 80.85%; the negative predictive value, 40.74%; and the OR was significant (2.90, $P = .0103$) (Table 1).

The Kruskal-Wallis test allowed rejecting the null hypothesis that the observed $\Delta$CVF in subjects with MS, OND, and HC originated from the same distribution ($P = .0003$). The post hoc test indicated the significant difference ($P < .01$) between patients with MS and HC and between subjects with MS and OND. HC versus subjects with OND was not statistically different (Fig 2).

The Kruskal-Wallis test applied to compare HC and MS subgroups (relapsing-remitting, primary-progressive, and secondary-progressive) indicated a significant difference ($P = .0014$), which was determined by relapsing-remitting versus HC ($P < .01$) and primary-progressive/secondary-progressive versus HC ($P < .05$). No statistically significant difference was assessed between the relapsing and progressive forms (Fig 3).
All the AUCs were different from one another—that is, the AUC was 0.7034 (standard error = 0.0564, \(P = .00015\)) in the comparison between MS and HC (ie, fairly accurate), 0.7306 (standard error = 0.0597, \(P = .00001\)) if the MS group was compared with OND (ie, fairly accurate), and 0.6323 (standard error = 0.0611, \(P = .0152\)) when comparing OND versus HC (ie, slightly accurate).

In the independent sample, \(\Delta CVF < 503.24\) was present in 41/52 patients with MS, 11/27 HC, and 4/10 subjects with OND (Table 2). Performance of the \(\Delta CVF\) model was also assessed on the independent sample (test set) by the analysis of the receiver operating characteristic analysis curve. The AUC was 0.7877 (standard error = 0.0505, \(z = 5.7018, P = .00015\)) in the comparison between MS and HC; the AUC was 0.8260 (standard error = 0.0591, \(z = 5.5162, P = 0\)) if the MS group was compared with OND; and the AUC was 0.55 (standard error = 0.1092, \(z = 0.4577, P = .3236\)) when comparing OND versus HC. There was significant difference in the AUC values for MS versus HC (\(z = 9.7015, P = 0\)), MS versus OND (\(z = 9.1021, P = 0\)), and HC versus OND (\(z = 3.7631, P = .000083\)). The accuracy of the model was fair for the comparison between MS and HC and MS and OND, while it was not informative between OND and HC.

The criterion \(\Delta CVF < 503.24\) applied within the MS subgroups to assess their capability to classify relapsing forms versus progressive forms resulted in 29/40 for relapsing-remitting and 10/14 for primary-progressive and secondary-progressive, with OR = 1.0545, not significantly different from 1 (\(P = .2674\)).

The logistic regression was applied to predict the realization of the variable \(\Delta CVF\) dichotomized according to the cut-off value, as a function of the demographic (age and sex) and clinical (Expanded Disability Status Scale; EDSS) regressors.

The implementation of the logistic model on the MS, HC, and OND groups did not result in the identification of significant effects of age, sex, and clinical status over the outcomes of \(\Delta CVF\). The \(P\) values corresponding to these considered variables for MS, HC, and OND were respectively: \(P_{\text{age}} = .81; P_{\text{sex}} = .79; P_{\text{EDSS}} = .75\), \(P_{\text{age}} = .77; P_{\text{sex}} = .56\), and \(P_{\text{age}} = .86; P_{\text{sex}} = .82\).

**DISCUSSION**

The cerebral venous system has very variable anatomic patterns,\(^{28–31}\) to maintain an efficient and normal CVF. Qualitative (ie, jugular valves or flow characteristics) and quantitative (ie, flow rate and velocity) aspects of CVF are demonstrated by using quantitative...
patients without any venous malformations. A possible explanation is that the active tension imparted by the smooth muscle layer of the veins is not sufficient to overcome transmural pressure. In the supine position, a lower venous wall tone is not sufficient to hold venous outflow, while in the sitting position, the physiologic collapse of the main drainage veins (ie, internal jugular veins) always overcomes the low vein wall tone. This deregulation might be due to a reduced responsiveness of the vessel wall because homeostasis might be lost in changing positions. Previous observations suggested that the autonomic nervous system may be intimately linked with the disordered immune regulation in MS. Vasoactive factors such as endothelin-1 and nitric oxide may play a role in the responsiveness of the vessel wall.33–38

Another possible explanation is that this abnormal venous response is secondary to white matter hypoperfusion, and its possible mechanisms and pathophysiology were reported by De Keyser et al.39

### CONCLUSIONS

The present study showed that a cutoff of abnormal CVF could discriminate patients with MS from those with OND and HC.

### ACKNOWLEDGMENTS

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### REFERENCES


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**Table 2: Analysis of classification errors: out-of-sample sets**

<table>
<thead>
<tr>
<th></th>
<th>MS vs HC</th>
<th>MS vs OND</th>
<th>OND vs HC</th>
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<tr>
<td><strong>Sen %</strong></td>
<td>78.85</td>
<td>91.11</td>
<td>40</td>
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<tr>
<td><strong>95% CI (Sen)</strong></td>
<td>67.75–89.95</td>
<td>82.80–99.43</td>
<td>9.64–70.36</td>
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<tr>
<td><strong>Spe %</strong></td>
<td>59.26</td>
<td>35.29</td>
<td>59.26</td>
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<tr>
<td><strong>95% CI (Spe)</strong></td>
<td>40.73–77.79</td>
<td>12.58–58.01</td>
<td>40.73–77.79</td>
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<tr>
<td><strong>FP %</strong></td>
<td>40.74</td>
<td>64.71</td>
<td>40.74</td>
</tr>
<tr>
<td><strong>95% CI (FP)</strong></td>
<td>22.21–59.27</td>
<td>41.99–87.42</td>
<td>22.21–59.27</td>
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<td><strong>FN %</strong></td>
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<td>8.89</td>
<td>60</td>
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<tr>
<td><strong>95% CI (FN)</strong></td>
<td>10.05–32.25</td>
<td>0.57–77.20</td>
<td>29.64–90.36</td>
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<td><strong>PPV %</strong></td>
<td>78.85</td>
<td>78.85</td>
<td>26.67</td>
</tr>
<tr>
<td><strong>95% CI (PPV)</strong></td>
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<td>67.75–89.95</td>
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<tr>
<td><strong>NPV %</strong></td>
<td>59.26</td>
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<tr>
<td><strong>95% CI (NPV)</strong></td>
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<td>29.64–90.36</td>
<td>54.12–91.34</td>
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<td><strong>OR</strong></td>
<td>5.42</td>
<td>5.59</td>
<td>0.97</td>
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<td><strong>95% CI (OR)</strong></td>
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<td>1.34–23.34</td>
<td>0.22–4.26</td>
</tr>
</tbody>
</table>

**Note:** Sen indicates sensitivity; Spe, specificity; FP, false-positive; FN, false-negative; NPV, negative predictive value; PPV, positive predictive value.

*The columns refer to each comparison between the groups in the independent samples.*
CCSVI not leaving a trace in MS. *J Neurol Neurosurg Psychiatry* 2011;82:436 – 40