In 1978, Jannetta and Gendell introduced the concept of neurogenic hypertension caused by pulsatile vascular compression of the left RVLM. In 1985, Jannetta et al. published the results of their study of 53 hypertensive patients with symptomatic cranial neuralgias, 51 of whom had compression of the left lateral medulla by arterial branches of the left vertebral artery. Of these 51 patients, 42 underwent microvascular decompression at the left RVLM; in 36 patients, the procedure was considered to be surgically adequate. Blood pressure normalized in 32 (89%) of these 36 patients. Similar findings were observed in only 2 (4%) of 50 normotensive control patients.

Animal models have defined the role of the sympathetic excitatory neurons of the RVLM and the inhibitory neurons of the caudal VLM in blood pressure regulation. The C1 adrenergic neurons in the RVLM have a major efferent pathway to the preganglionic sympathetic neurons in the spinal cord. In animal studies in which the RVLM was electrically or chemically stimulated, vasoconstriction and hypertension could be induced. Bilateral inhibition or chemical destruction resulted in hypotension.

Magnetic resonance imaging, CT scanning, and angiographic techniques have been used to evaluate the presence of neurovascular compression in patients with hypertension. However, the role of these techniques in the diagnosis of neurovascular compression remains controversial.

Several studies have suggested that neurovascular compression (NVC) of the brainstem might be a cause of hypertension. Because this compression syndrome might be demonstrated by MR imaging studies, several authors have tried to assess its prevalence in small series of patients with hypertension. This article presents a meta-analysis of these studies.

Methods. The studies reviewed by the authors were based on MR imaging and included the presence of left-sided NVC of the left rostral ventrolateral medulla oblongata (RVLM) and/or the cranial nerves IX and X root entry zone in patients with apparent primary hypertension compared with normotensive patients. Several studies also included patients with secondary hypertension as an additional control group, which is analyzed separately.

Results. Meta-analysis included data from 14 studies (597 patients with primary hypertension and 609 controls). The effect size was OR 2.68 (95% CI 1.51–4.75, p = 0.001) (random effect), which is consistent with the hypothesis that NVC of the left RVLM is more frequent in patients with apparent primary hypertension compared with normotensive individuals. Stratification for the study design revealed an effect size for prospective studies of OR 1.97 (95% CI 0.74–5.30, p = 0.178) and for retrospective studies of OR 3.36 (95% CI 1.66–6.79, p = 0.001).

Conclusions. This meta-analysis indicates a statistically significant effect size for left-sided NVC in apparent primary hypertension. However, this effect is absent if subanalysis is confined to prospective studies.

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ography have been used to assess NVC. Of these, MR imaging is noninvasive and is the most sensitive technique by which a relationship between vascular structures and the RVLM can be assessed.\(^2\) The relationship between NVC of the left-sided RVLM and hypertension remains controversial, however. Initially, some MR imaging studies reported statistically significant differences in NVC of the RVLM in hypertensive patients compared with normal controls (for example, Naraghi et al.,\(^1\) Akimura et al.,\(^1\) and Colón et al.\(^4\)). More recently, other studies have failed to replicate these findings (Zizka et al.,\(^2\) and Thuerl et al.,\(^2\) among others\(^2,11,17\)). Apart from the comparison with normotensive individuals, some studies also compared their results to patients with secondary hypertension.\(^1,6,15\) This was done to discriminate if the NVC or vascular elongation could be the consequence of the hypertension itself rather than the cause.

Postulated by Jannetta et al.,\(^10\) the effect of NVC on the blood pressure was lateralized to the left. Left lateralization of cardiovascular control was explained by the prevailing influence of afferent signals arriving via the left vagal nerve from mechanoreceptors of the left atrium. However, this lateralization is debated by Morimoto et al.\(^15\)

Meta-analysis allows for the integration of studies and enhances statistical power in the estimation of the true population effect size. This article presents a meta-analysis of left-sided NVC in relation to apparent primary hypertension. The checklist proposed by Stroup et al.\(^22\) was used as a guideline for this meta-analysis.

**Methods**

**Sample of Studies**

Studies were identified through literature searches of MEDLINE by using the website at the National Library of Medicine. The searches were based on the following medical subject heading categories: “hypertension,” “neurogenic,” “primary,” “essential,” “neurovascular,” “compression,” “medulla oblongata,” “RVLM,” “cranial nerves,” “magnetic resonance imaging,” “vagal nerve,” and “glossopharyngeal nerve.” These terms were also used for the search in Embase. The search was conducted in November 2009. Search strategies and results are given in Table 1. Titles and abstracts were evaluated for appropriateness for this study. Case reports, review articles, and letters were excluded from the list. Additional articles were identified from the references of relevant studies and review articles. After a review of the articles, with consideration of the inclusion and exclusion criteria as discussed below, 14 studies were selected for inclusion in the meta-analyses.\(^1,2,4,6,7,11,15-18,20,21,23,24\) Selected studies were published between 1994 and 2007. All studies included in the meta-analyses were independently reviewed and evaluated by 2 of the authors of this study (H.B. and T.M.) to obtain consensus on inclusion criteria and quantifiable data.

**Inclusion and Exclusion Criteria for Studies**

Studies have been included in which the presence of left-sided NVC was investigated using MR imaging in patients with primary hypertension compared with normotensive controls. Both retrospective and prospective studies were included. Studies in other European languages apart from English were also evaluated. The studies had to include sufficient quantitative information for the computation of an effect size (see **Effect Sizes** below). Study duplicates were excluded, taking the most accurate or recent study (that is, Schmitz et al.\(^19\) and Hohenbleicher et al.,\(^3\) and Ceral et al.\(^2\) and Zizka et al.\(^20\)). One study did not have sufficient information to calculate an effect size.\(^3\)

**Effect Sizes**

Comprehensive Meta-Analysis software (version 2.2.046, 2007; Biostat, Inc.) was used for statistical analysis. The effect size used was the odds ratio of NVC in hypertensive patients compared with normotensive patients. A pooled odds ratio and 95% confidence intervals were constructed. The significance of the overall odds ratio was determined by the \(z\)-test. For sensitivity analysis, each study was removed in turn from the total, and the remainders were reanalyzed. The type I error was set at 0.05. The tests were 2-tailed.

**Fixed-Effects Model Versus Random-Effects Model**

Both the fixed-effects and the random-effects models were used to evaluate hypertension in relation to NVC. Heterogeneity \(Q\) tests were performed. If heterogeneity existed, the random-effects model, which yields wider confidence intervals, was adopted.

**Publication Bias and Funnel Plot**

Publication bias tends to occur if only significant findings are published. To estimate whether publication bias exists, a “funnel plot” was created. If there is a publication bias in the data, few points will appear around the point estimate indicating no effect (OR 1.0) for studies with large standard errors.\(^14\)

**Moderators of Effect Sizes**

Various study characteristics can influence the effect size, and can be assessed by stratification, as follows: design (prospective vs retrospective); blinding for the presence of hypertension (yes/no); MR imaging technique (magnet strength in Teslas, constructive interference in steady-state sequences, 3D imaging, time of flight sequences); definition of neurovascular contact; definition of REZ or RVLM; and the definition of hypertension used. Also, the study year (more recent studies have more advanced MR imaging techniques and generally have more advanced methodology), percent male (to allow for assessment of gender effects), and age (older patients are more likely to have hypertension and elongated, tortuous vessels) are effect modifiers.

**Results**

Patient characteristics in the 14 studies are given in Table 2. Data from 597 patients with primary hypertension and 609 normotensive individuals contributed to the meta-analysis. Seven studies used an additional control...
group of patients with secondary hypertension (total 88). The average sample size per study for the primary hypertension group was 45.9 patients, compared with an average size of 43.5 in the control group (normotensive individuals). The secondary hypertension group had an average size of 12.6 patients. The average percentage of male patients across these studies was 50% for the primary hypertension group and 48.5% for the normotension group. The secondary hypertension group had data on sex in only 5 of the 7 studies: 47.9% of patients were male. The mean age (± SD; available in 11 studies) of patients with primary hypertension varied among studies—between 34 ± 7 years and 61 ± 12.5 years compared with 43 ± 9 years and 52 ± 15.8 years in the normotension group. The age in the secondary hypertension group ranged from 41 ± 12 years to 56.7 ± 10.3 years in 6 studies. Within each study there were no statistical differences regarding age between the hypertension and normotension or secondary hypertension groups, nor were there any statistical differences in sex within each group.

Table 3 gives an overview of the presence or absence of NVC. Of the 14 studies, 7 reported a difference, including 1 study (Smith et al.21) that presented the results only between given subgroups. The overall analysis of the primary hypertension and normotension groups showed that NVC was present in 260 (43.6%) of 597 patients and in 172 (28.2%) of 609 patients, respectively. Meta-analysis of those 14 studies revealed an overall OR of 1.77 (95% CI 1.35–2.32) for a fixed-effects model and an OR of 2.68 (95% CI 1.51–4.75) for a random-effects model (Fig. 1). The test for heterogeneity reveals a Q value of 49.7 (df 13; p < 0.001), which indicates that a random-effects model is more appropriate. Sensitivity analysis did not change the results. A funnel plot indicates a possible publication bias (Fig. 2). For all other odds ratios in this analysis, the random effect was used because it was more appropriate.

**TABLE 1: Search terms and number of results for articles on hypertension**

<table>
<thead>
<tr>
<th>Search No.</th>
<th>Medical Subject Heading Categories</th>
<th>PubMed</th>
<th>Embase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>([hypertension] AND magnetic resonance imaging) AND neurovascular compression</td>
<td>46</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>([hypertension] AND magnetic resonance imaging) AND RVLM</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>([hypertension] AND magnetic resonance imaging) AND medulla oblongata</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>([hypertension] AND magnetic resonance imaging) AND essential</td>
<td>219</td>
<td>373</td>
</tr>
<tr>
<td>5</td>
<td>([hypertension] AND magnetic resonance imaging) AND primary</td>
<td>422</td>
<td>851</td>
</tr>
<tr>
<td>6</td>
<td>([hypertension] AND magnetic resonance imaging) AND neurogenic</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>([hypertension] AND magnetic resonance imaging) AND vagal nerve</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>([hypertension] AND magnetic resonance imaging) AND glossopharyngeal nerve</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>([hypertension] AND magnetic resonance imaging) AND cranial nerves</td>
<td>102</td>
<td>36</td>
</tr>
</tbody>
</table>

**TABLE 2: Literature review of studies of hypertension—patient characteristics**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Pts w/ PHT</th>
<th>Controls</th>
<th>SHT (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% Males</td>
<td>Mean Age</td>
</tr>
<tr>
<td>Naraghi et al., 1994</td>
<td>24</td>
<td>62.5</td>
<td>48 ± 13</td>
</tr>
<tr>
<td>Akimura et al., 1995</td>
<td>32</td>
<td>40.6</td>
<td>57.6 ± 7</td>
</tr>
<tr>
<td>Watters et al., 1996</td>
<td>60</td>
<td>66.7</td>
<td>NR</td>
</tr>
<tr>
<td>Morimoto et al., 1997</td>
<td>21/20†</td>
<td>57.1</td>
<td>58 ± 12</td>
</tr>
<tr>
<td>Colón et al., 1998</td>
<td>30</td>
<td>50.0</td>
<td>50.9 ± 12.4</td>
</tr>
<tr>
<td>Giuffrida et al., 1998</td>
<td>17</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Johnson et al., 2000</td>
<td>38</td>
<td>55.3</td>
<td>61 ± 12.5</td>
</tr>
<tr>
<td>Morise et al., 2000</td>
<td>23</td>
<td>73.9</td>
<td>52.1 ± 2.7</td>
</tr>
<tr>
<td>Thuerl et al., 2001</td>
<td>33</td>
<td>45.5</td>
<td>52 ± 15.5</td>
</tr>
<tr>
<td>Hohenbleicher et al., 2001</td>
<td>125/115‡</td>
<td>47.0</td>
<td>54 ± 13</td>
</tr>
<tr>
<td>Ságglitz &amp; Gaab, 2002</td>
<td>25</td>
<td>NR</td>
<td>53 ± 9</td>
</tr>
<tr>
<td>Smith et al., 2004</td>
<td>45</td>
<td>53.3</td>
<td>NR</td>
</tr>
<tr>
<td>Sendeski et al., 2006</td>
<td>64</td>
<td>NR</td>
<td>34 ± 7</td>
</tr>
<tr>
<td>Ceral et al., 2007</td>
<td>71</td>
<td>54.9</td>
<td>52.5 ± 11.5</td>
</tr>
</tbody>
</table>

* The mean age is expressed as years ± SD. Abbreviations: excl = excluded; ND = not done; NR = not reported; NT = normotension; PHT = primary hypertension; Pts = Patients; SHT = secondary hypertension.
† Patient excluded, but data on 21 patients.
‡ Patients excluded due to technical failure and lack of consensus agreement.
A meta-analysis of the primary hypertension group compared with the secondary hypertension group reveals an OR of 6.72 (95% CI 1.54–29.40) (Fig. 3).

The presence of right-sided compression has been registered in 11 studies. A meta-analysis of right-sided NVC also reveals a significantly elevated OR of 1.82 (95% CI 1.28–2.57). An analysis of left-sided and/or right-sided compression also reveals an OR of 3.92 (95% CI 1.88–8.20); however, the results are distorted due to 4 studies with ORs ranging from 12 to 161.

**Subgroup Analysis**

Inclusion and/or exclusion criteria were reported in 11 studies, including 1 in which only older age (> 75

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naraghi et al., 1994</td>
<td>65.000</td>
<td>6.518</td>
<td>648.236</td>
<td>3.557</td>
<td>0.000</td>
</tr>
<tr>
<td>Akimura et al., 1995</td>
<td>17.857</td>
<td>3.999</td>
<td>79.737</td>
<td>3.775</td>
<td>0.000</td>
</tr>
<tr>
<td>Watters et al., 1996</td>
<td>1.070</td>
<td>0.520</td>
<td>2.200</td>
<td>0.184</td>
<td>0.854</td>
</tr>
<tr>
<td>Morimoto et al., 1997</td>
<td>25.160</td>
<td>1.329</td>
<td>476.426</td>
<td>2.149</td>
<td>0.032</td>
</tr>
<tr>
<td>Colon et al., 1998</td>
<td>0.536</td>
<td>0.202</td>
<td>1.424</td>
<td>-1.251</td>
<td>0.211</td>
</tr>
<tr>
<td>Giuffrida et al., 1998</td>
<td>27.500</td>
<td>2.883</td>
<td>262.337</td>
<td>2.880</td>
<td>0.004</td>
</tr>
<tr>
<td>Johnson et al., 2000</td>
<td>1.527</td>
<td>0.724</td>
<td>3.220</td>
<td>1.113</td>
<td>0.266</td>
</tr>
<tr>
<td>Morise et al., 2000</td>
<td>9.396</td>
<td>2.528</td>
<td>34.920</td>
<td>3.345</td>
<td>0.001</td>
</tr>
<tr>
<td>Thuerl et al., 2001</td>
<td>1.020</td>
<td>0.360</td>
<td>2.885</td>
<td>0.037</td>
<td>0.971</td>
</tr>
<tr>
<td>Hohenbleicher et al., 2001</td>
<td>1.578</td>
<td>0.781</td>
<td>3.187</td>
<td>1.271</td>
<td>0.204</td>
</tr>
<tr>
<td>Saglitz et al., 2002</td>
<td>1.871</td>
<td>0.635</td>
<td>5.512</td>
<td>1.137</td>
<td>0.256</td>
</tr>
<tr>
<td>Smith et al., 2004</td>
<td>1.875</td>
<td>0.692</td>
<td>5.077</td>
<td>1.237</td>
<td>0.216</td>
</tr>
<tr>
<td>Sendeski et al., 2006</td>
<td>6.741</td>
<td>1.850</td>
<td>24.564</td>
<td>2.892</td>
<td>0.004</td>
</tr>
<tr>
<td>Ceral et al., 2007</td>
<td>0.930</td>
<td>0.447</td>
<td>1.936</td>
<td>-0.193</td>
<td>0.847</td>
</tr>
</tbody>
</table>

**Figure 1.** Overall meta-analysis of hypertensive versus normotensive patients. The last entry represents the overall values. EHT = essential hypertension group; NT = normotension group.
Neurovascular compression in hypertension

A cumulative meta-analysis (in which the studies are chronologically arranged and the effect of each study is calculated by combining the results of previous studies) had a declining effect, to an OR of 2.68 (95% CI 1.51–4.75) (Fig. 5).

Across the studies, different MR imaging techniques have been used, apart from the magnet strength in Teslas (reported in all but 1 study, and in 11 studies a 1.5-T unit was used) and section thickness; especially the use of MR angiography and/or 3D MR imaging sequences is considered important to investigate the presence of neurovascular contact.22 Grouping the studies by using one or both of the latter techniques (OR 3.88, 95% CI 1.79–8.41) versus none (OR 1.42, 95% CI 0.63–3.21) indicates no effect in studies with limited visualization.

The definition of neurovascular contact was given in 13 studies (including 1 extracted from a duplicate study), and in 4 it was divided into subgroups of simple contact, contact with compression/displacement, and brainstem deformity (Table 4). We considered “contact” with or without any other form of compression as the most consistent between studies (for example, Watters et al.;24 Grades II and III). The RVLM and/or REZ of cranial nerves IX and X was only precisely defined in 2 studies and at best moderately defined in 2 others.2,7,18,21 Statistical analysis of these 4 studies revealed an OR of 1.41 (95% CI 0.93–2.13).

In 12 studies, normotension was defined as a blood pressure < 140/90 mm Hg, whereas hypertension was defined by different values, from > 140/90 mm Hg to ≥ 180/110 mm Hg (Table 4). Seven studies refer to the WHO or International Society of Hypertension guidelines for hypertension. The definitions are considered comparable except in the study of Ceral et al.,2 in which hypertension was defined as a relatively high blood pressure, ≥ 180 mm Hg systolic and/or ≥ 110 mm Hg diastolic. Analyzing the data without this study did not change the results (OR 3.04, 95% CI 1.63–5.64). Secondary hypertension was excluded from the primary hypertension by reporting investigations and/or causes of the secondary hypertension in all studies.
<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Prosp/Retro</th>
<th>Blinding</th>
<th>Definition of NVC</th>
<th>Definition of PHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naraghi et al., 1994</td>
<td>NR</td>
<td>previous neurological disease, intracerebral hemorrhage, &amp; CN disorders</td>
<td>prosp</td>
<td>yes</td>
<td>visible vascular loop on T2-weighted MRI or on MRA, w/ its convexity impinging on VLM at REZ level of CNs IX &amp; X</td>
<td>per WHO, BP &gt;160/95 mm Hg, on independent occasions, requiring continuous meds; renovascular HT, aldosteronism, Cushing syndrome, &amp; pheochromocytoma excl by appropriate tests</td>
</tr>
<tr>
<td>Akimura et al., 1995</td>
<td>PHT/SHT grp referred from cardiology</td>
<td>excl pts &gt;70 yrs of age</td>
<td>retro</td>
<td>no</td>
<td>when hyperintensities were obviously contiguous w/ medulla or nerve REZ; deformity of medulla was not necessary to define NVC</td>
<td>NR (BP &gt;150/80 mm Hg) (meds)</td>
</tr>
<tr>
<td>Watters et al., 1996</td>
<td>pts undergoing Tx for HT, by audit of computerized medical records, cross-reference for MR imaging; NR for NT grp</td>
<td>pts w/ renal or endocrine sources of HT excl; NR for NT grp</td>
<td>retro</td>
<td>no</td>
<td>I, contact only; II, contact &amp; depression of lat medulla; III, displacement or rotation of medulla</td>
<td>pts w/ renal or endocrine sources of HT excl</td>
</tr>
<tr>
<td>Morimoto et al., 1997</td>
<td>&gt;75 yrs of age</td>
<td>prosp</td>
<td>yes</td>
<td>NR</td>
<td></td>
<td>per 1993 WHO/ISH (BP &gt;140/90 mm Hg) (meds)</td>
</tr>
<tr>
<td>Colón et al., 1998</td>
<td>all evaluated at UM’s HT clinic; controls from grp of pts undergoing brain MRI during same period</td>
<td>pts w/ SHT &amp; pregnant women</td>
<td>prosp</td>
<td>yes</td>
<td>1, no contact; 2, contact w/o compression; 3, contact w/ compression &amp; associated brainstem deformity</td>
<td>BP &gt;149/90 mm Hg (WHO Committee on Hypertension Guidelines, 1993) on 3 successive visits, or meds use for previously documented PHT; known causes of HT (renovascular or pheochromocytoma) excl</td>
</tr>
<tr>
<td>Giuffrida et al., 1998</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>adopted from Watters et al.: Grade II</td>
<td>per WHO, BP &gt;160/95 mm Hg; pathology causing HT was excl (meds)</td>
</tr>
<tr>
<td>Johnson et al., 2000</td>
<td>NR</td>
<td></td>
<td>retro</td>
<td>yes</td>
<td>vascular signal void in contact w/ junction of exiting nerve root bundle &amp; adjacent medulla oblongata; 1, no contact; 2, contact, compression, or deformity</td>
<td>NR</td>
</tr>
<tr>
<td>Morise et al., 2000</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>yes</td>
<td>visible vascular loop on T2-weighted MRI or on MRA, w/ its convexity impinging on VLM at REZ level of CNs IX &amp; X</td>
<td>BP &gt;160/90 mm Hg in sitting position on 2 separate occasions, excl SHT on routine screening tests (no meds)</td>
</tr>
<tr>
<td>Thuerl et al., 2001</td>
<td>NR</td>
<td>renovascular, renal parenchymal, &amp; endocrine causes of HT excl</td>
<td>prosp</td>
<td>yes</td>
<td>adopted from Watters et al.</td>
<td>BP &gt;140/90 mm Hg w/o meds, or if lower, treated w/ antihypertensive meds (WHO Committee on Hypertension Guidelines, 1999)</td>
</tr>
<tr>
<td>Hohenbleicher et al., 2001</td>
<td>controls from genetically unrelated individuals identified through pts &amp;/or announcements; NR for pts (from HT clinic)</td>
<td>SHT</td>
<td>NR</td>
<td>yes</td>
<td>arterial vessel or vascular loop w/ its convexity touching surface of lt REZ</td>
<td>Rx for antihypertensive meds &amp;/or avg 24-hr ambulatory BP level =140/90 mm Hg; SHT ruled out by appropriate physical &amp; laboratory evaluation</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Prosp/ Retro Blinding</th>
<th>Definition of NVC</th>
<th>Definition of PHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Säglitz &amp; Gaab, 2002</td>
<td>NT grp randomly chosen from pts undergoing lumbar disc Tx; NR for PHT &amp; SHT grps</td>
<td>NR</td>
<td>prosp NR</td>
<td>adopted from Akimura et al: IRTSE sequences, vascular flow-void signal directly contiguous w/ surface of REZ in axial plane; no differentiation made btwn vascular contacts w/ &amp; w/o associated brainstem deformity</td>
<td>WHO criteria; SHT excl (meds)</td>
</tr>
<tr>
<td>Smith et al., 2004</td>
<td>NR no MRI due to claustrophobia; inability to obtain stable microelectrography; complicated or SHT, arrhythmia, or chronic disease</td>
<td>retro yes</td>
<td>absence of “black” CSF btwn “white” of blood vessel &amp; “gray” of lt-hand side of medulla w/in 10 mm of pontomedullary junction</td>
<td>WHO Joint National Committee: at least 3 recordings in seated position on separate occasions in clinical setting—PHT-1, BP 140/90–159/99 mm Hg; PHT-2/3, BP ≥160/100 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Sendeski et al., 2006</td>
<td>PHT grp from outpatients of HT unit; NT grp from employees of institution</td>
<td>SHT, history of arterial disease, impossibility of performing MRI</td>
<td>NR NR</td>
<td>I, image of vessel in contact w/ RVLM but not compressing it; II, evident compression of RVLM by a vessel</td>
<td>repeated BP measurements &gt;140/90 mm Hg or by use of antihypertensive meds w/ normal BP &amp; a history of HT</td>
</tr>
<tr>
<td>Ceral et al., 2007</td>
<td>NR</td>
<td>SHT</td>
<td>prosp yes</td>
<td>NR (simple contact of artery w/ brainstem or an impression of the artery that produced an apparent deformity of the brainstem contour; from duplicate publication, Zizka et al.)</td>
<td>HT &gt;2 yrs, ≥3 meds, systolic BP ≥180 mm Hg &amp;/or diastolic BP ≥110 mm Hg</td>
</tr>
</tbody>
</table>

* avg = average; BP = blood pressure; CN = cranial nerve; grp = group; HT = hypertension; IRTSE = inversion recovery turbo spin echo; ISH = International Society of Hypertension; meds = medications; MRA = MR angiogram; prosp = prospective; retro = retrospective; UM = University of Michigan.
Discussion

Our meta-analysis suggests a positive association (OR 2.68, 95% CI 1.51–4.75) between primary hypertension and NVC of the left-sided medulla oblongata on MR imaging. After the initial promising results of Naraghi et al.17 in 1994, several studies replicated these results. However, since 2000, only 2 of 8 studies found a moderate effect. A cumulative meta-analysis confirms this impression. The additional control group of patients with secondary hypertension does suggest that the presence of NVC in patients with apparent primary hypertension is not the result of elongation of the vessels due to hypertension. Unfortunately, the number of patients in each study of secondary hypertension is small, and no NVC distorts the odds ratio to confirm this mechanism. Grouping in studies according to better methodology (prospective and with blinding) does not show or only weakly shows an effect. Analysis of NVC on the left side compared with the right side revealed a higher odds ratio for left-sided com-
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This might confirm the postulated lateralization of the blood pressure regulation center on the left side of the medulla oblongata.

In this meta-analysis we used the random-effects model. This model accounted for additional sources of interstudy variation when heterogeneity existed. It was more conservative than the fixed-effects model, because that model assumes the same true effects between studies, whereas the random-effects model assumes the normally distributed effects and gives parameters for the interstudy variation.

Uniform use of standardized criteria for the definition of MR imaging techniques, NVC, RVLM/REZ, hypertension, normotension, and secondary hypertension are important.

Beyond the Meta-Analysis

The results indicate that there is a possible relationship between NVC on MR imaging studies and primary hypertension. It can be questioned whether MR imaging is adequate to visualize the vasculature and relationship with the brainstem. Surgical reports on microvascular decompression for the treatment of hypertension indicate that some patients might benefit from this intervention.\(^{5,12}\) It remains to be investigated how patients need to be selected. Subsequently, the relatively acute risks and potential benefits of microvascular decompression need to be weighed against the chronic morbidity and the risk of death associated with systemic hypertension. Levy et al.\(^{13}\) reported in 2001 on their multinstitutional, randomized, prospective trial with specific end points, which is in progress. They will prospectively assign 80 hypertensive patients who are currently receiving 3 or more antihypertensive medications to surgery (regardless of MR imaging findings) or continued medical therapy (40 in each group). As of this writing there has been no publication of their results.

Conclusions

The overall result of this meta-analysis indicates that the left-sided NVC syndrome is more prevalent in patients with apparent primary hypertension. However, this effect is absent if subanalysis is confined to prospective studies.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Boogaarts, Menovsky, de Vries. Acquisition of data: Boogaarts. Analysis and interpretation of data: Boogaarts. Drafting the article: Boogaarts. Critically revising the article: Boogaarts, Menovsky, de Vries, Lenders. Statistical analysis: Boogaarts, Verbeek. Study supervision: de Vries, Grotenhuis.

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