Arterial Compression of the Retro-Olivary Sulcus of the Ventrolateral Medulla in Essential Hypertension and Diabetes

Joyce S. Nicholas, Sabino J. D’Agostino, Sunil J. Patel

Abstract—Pulsatile arterial compression in the retro-olivary sulcus along the surface of the ventrolateral medulla has been postulated as a mechanism in both essential hypertension and diabetes. The objective of this study was to test the independent effect of arterial compression in the retro-olivary sulcus on each of these diseases, using separate logistic regression models to control for other known risk factors. Study design was case–control. The study population consisted of 147 consecutive patients treated for neurological conditions requiring MRI of the posterior cranial fossa. Information on essential hypertension, diabetes, and risk factors for each disease was abstracted from medical records. Presence of arterial compression was determined by blinded review of magnetic resonance images. In the essential hypertension analysis, odds of arterial compression among hypertensive patients were 2.99-times the odds among normotensive subjects ($P=0.04$), controlling for hypertension risk factors such as age, body mass index, race, diabetes, and family history of hypertension. Of compressed hypertensive subjects, 56% were compressed on the left and 44% were compressed on the right. In the diabetes analysis, odds of arterial compression among diabetic subjects were 1.14-times the odds among nondiabetic subjects ($P=0.83$). Of compressed diabetic subjects, 60% were compressed on the left, and 40% were compressed on the right. Results suggest that arterial compression of the retro-olivary sulcus may be an independent risk factor for essential hypertension in this population, supporting the postulate for a treatable (with microvascular decompression) neural mechanism for essential hypertension. However, in the diabetic population, the slight increase in the odds of arterial compression was not significant. *(Hypertension. 2005;46[part 2]:982-985.)*

Key Words: arterial compression ■ diabetes mellitus ■ hypertension, essential

A neurogenic basis for essential hypertension (EHTN) has been suggested for a subgroup of EHTN patients with chronic elevation of sympathetic tone.1–6 Animal studies confirm the presence of a subpial catecholamine synthesizing neuronal group (C-1) in the rostral ventrolateral medulla (VLM), which, when stimulated electrically, chemically, or mechanically, produces a transient pressor response.7–10 This neuronal group is an integral part of the medullary baroreflex pathway that also includes the nucleus tractus solitarius, caudal VLM, and caudal pressor area neuronal groups. Histochemical studies of human medullae obtained at autopsy show a similar population of catecholamine neurons in the subpial regions of the retro-olivary sulcus (ROS) near the root entry zone of the ninth and tenth cranial nerves.11,12 It is postulated that in neurogenic EHTN, pulsatile arterial compression (AC) of this subpial vasomotor neuronal network in the ROS induces a chronic overstimulation of the sympathetic nervous system and thus sustains elevated systemic arterial blood pressure through effects on the heart, peripheral vasculature, and kidney.13

Previous MRI and autopsy studies have shown an association between pulsatile AC of the VLM and EHTN; however, the reported prevalence has been inconsistent, as has been the laterality and exact location of vessel contact.5,14–23 To better address the question of location, our group has undertaken electrical stimulation studies to precisely define the placement of these sympatho-excitatory and inhibitory neuronal aggregates in humans24 and has applied this definition to the determination of AC status in the present study.

Relative to AC and EHTN, less information is available about AC and diabetes. However, a neurogenic basis has been suggested in the predisposition to insulin resistance and the development of type 2 diabetes. In particular, Jannetta et al25 proposed that arterial compression of the right lateral medulla may trigger in some patients a state of autonomic dysfunction including hyperactivity of pancreatic endocrine function. Autonomic enervation of omental fat comes from the right lateral medulla in animals. It has been postulated that elevated sympathetic tone through this innervation leads to breakdown of omental fat into metabolites such as triglycerides and free

Fatty acids. The resulting elevation of circulating as well as local concentrations of free fatty acids creates skeletal muscle and hepatic insulin resistance, potentially triggering the onset of insulin resistance and ultimately type 2 diabetes in susceptible individuals.25

The objective of the present study was to test the potential association of AC in the ROS with both EHTN and diabetes in a patient population. Existing clinical data were analyzed in a case–control design using logistic regression with EHTN and diabetes as outcomes in separate models. Multivariate techniques were used to evaluate the independent effect of AC in the ROS on each disease through control of other known risk factors.

Methods

The study design was case–control and was approved by the Medical University of South Carolina institutional review board. All data came from existing records. The study population consisted of consecutive patients treated at the Medical University of South Carolina hospital during 1993 to 2002 for disorders requiring MRI of the posterior cranial fossa as part of their diagnostic evaluation (disorders included trigeminal neuralgia, glossopharyngeal neuralgias, hemifacial spasm, atypical facial pain). These patients were selected because the existing imaging allowed assessment of AC in the ROS. EHTN status, diabetes status, and data on known risk factors for each disease were abstracted from medical records. EHTN was defined as documented systolic blood pressure >140 or a diastolic blood pressure >90 on 3 separate occasions, with no record of secondary causes of hypertension. The hypertensive group included subjects whose blood pressures were normalized on medications at the time of medical record review. None of the normotensive patients were using antihypertensive medications. All patients with interpretable imaging and complete clinical data were included.

The presence of AC in the ROS was determined by image review, with the reader (neurosurgeon) blinded to patient name, medical history, and EHTN/diabetes status. Based on our preliminary mapping studies,24 the ROS was defined as the sulcus just posterior to the olive and anterior to the exit of cranial nerves nine and ten. AC was defined as occurring if a vessel was observed contacting any portion (inferior to caudal) of the ROS (left and/or right side) (Figure). Any type of arterial contact with neural tissue, whether this was indenting the surface of the medulla or simply touching it, was considered as arterial compression. To assure reliable determination of AC status, a randomly selected sample of images was evaluated by a second reader (neuroradiologist) using these same criteria. The resulting kappa score was 0.846 (P=0.001), indicating excellent agreement between readers (kappa is a measure of inter-rater reliability in which scores >0.75 indicate excellent agreement).

Data were analyzed using logistic regression with EHTN status as the outcome in one model and diabetes status as the outcome in a second model. The primary predictor variable in both models was AC. Clinically prespecified risk factors for hypertension (age, body mass index [BMI], race, gender, diabetes, and family history of hypertension) were compared between hypertensive and normotensive subjects using t tests for continuous variables and x² tests for categorical variables. Similar comparisons were made for diabetic and nondiabetic subjects using clinically prespecified risk factors for diabetes (age, BMI, and gender). Family history of diabetes was not included because of the small number of patients for whom this information was available. The strategy for multivariate model building was to enter clinically relevant covariates if found to differ between groups in the univariate analyses, using P<0.2 as a guide to entry. To avoid bias in the estimate of regression coefficients, the number of entered variables was restricted such that the events per variable would be ≥10 for either group (Monte Carlo simulations indicate that an events per variable value ≥10 is sufficient to prevent potentially misleading associations26). All calculations were made using SPSS software. Logistic regression is an established method for determining the independent association between an outcome variable and several predictor variables. The resulting measure (odds ratio) can be interpreted, in the EHTN model, as the odds of AC among hypertensive subjects relative to normotensive subjects, controlling for the potential effects of clinically relevant covariates found to differ between hypertensive and normotensive study groups. A similar interpretation applies to the diabetes model.

Results

In the EHTN multivariate analysis, the odds of AC among hypertensive subjects were 2.99-times the odds among normotensive subjects (95% confidence interval [CI], 1.04 to 8.58), controlling for effects of hypertension risk factors age, BMI, race, diabetes, and family history of hypertension. Gender was not added to the multivariate model because it did not differ between hypertensive and normotensive groups in univariate analyses. There were 60 hypertensive subjects and 79 normotensive subjects included in univariate analyses, with 42% and 29% compressed, respectively. The multivariate model was based on 114 patients with complete data on all entered variables (Tables 1 and 2). Of the compressed hypertensive subjects, 56% were compressed on the left and

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive Subjects</th>
<th>Normotensive Subjects</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial compression</td>
<td>25 (42)</td>
<td>23 (29)</td>
<td>0.150</td>
</tr>
<tr>
<td>Age</td>
<td>65 (mean)</td>
<td>56 (mean)</td>
<td>0.000</td>
</tr>
<tr>
<td>Body mass index</td>
<td>30 (mean)</td>
<td>26 (mean)</td>
<td>0.000</td>
</tr>
<tr>
<td>Race (black)</td>
<td>10 (17)</td>
<td>5 (6)</td>
<td>0.059</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>26 (43)</td>
<td>32 (41)</td>
<td>0.862</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (17)</td>
<td>3 (4)</td>
<td>0.018</td>
</tr>
<tr>
<td>Family history</td>
<td>36 (62)</td>
<td>27 (37)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*Univariate difference between groups based on chi square tests for categorical variables and t tests for continuous variables.
44% were compressed on the right. In the diabetes analysis, the unadjusted odds of AC among diabetic subjects were 1.14-times the odds among nondiabetic subjects (95% CI, 0.36 to 3.63; not significant). The only significant predictor variable in univariate analyses was BMI ($P=0.02$). There were 14 diabetic subjects and 119 nondiabetic subjects included in univariate analyses, with 36% and 33% compressed, respectively. No multivariate analyses were performed because unbiased regression estimates could not be assured based on only 14 cases (Tables 3 and 4). Of the 5 compressed diabetic subjects, 3 (60%) were compressed on the left and 2 (40%) were compressed on the right.

### Discussion
Mechanical irritation from pulsatile compression by an artery is known to be the pathogenic mechanism responsible for disease states such as trigeminal neuralgia, glossopharyngeal neuralgia, and hemifacial spasm. A similar pathogenic mechanism has long been postulated for EHTN and more recently for diabetes.

Results of this study suggest that AC in the ROS may be a risk factor for EHTN in this study population, independent of the known effects of the hypertension risk factors age, BMI, race, diabetes, and family history of hypertension. In the diabetic population, the slight increase in the unadjusted odds of AC was not statistically significant; however, it should be noted that the small number of diabetes cases (14) yielded low statistical power and precluded adjustment for potential effects of other risk factors. Further analysis of a larger group of patients is needed to better assess the role of AC in diabetes.

### Table 2. Logistic Regression Results for Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Multivariate Odds Ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial compression</td>
<td>1.74 (0.86–3.53)</td>
<td>2.99 (1.04–8.58)</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (1.02–1.07)</td>
<td>1.08 (1.04–1.13)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.13 (1.05–1.21)</td>
<td>1.28 (1.13–1.44)</td>
</tr>
<tr>
<td>Race (black)</td>
<td>2.96 (0.95–9.18)</td>
<td>1.54 (0.31–7.67)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.10 (0.56–2.17)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.76 (1.25–18.20)</td>
<td>1.55 (0.21–11.49)</td>
</tr>
<tr>
<td>Family history</td>
<td>2.85 (1.40–5.80)</td>
<td>10.73 (3.17–36.28)</td>
</tr>
</tbody>
</table>

*Gender was not included in the multivariate analysis because it did not differ between groups in the univariate analysis. The multivariate model is based on 114 patients with complete data on all included variables.

### Table 4. Logistic Regression Results for Diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial compression</td>
<td>1.14 (0.36–3.63)</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.97–1.05)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.10 (1.01–1.20)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>0.54 (0.16–1.84)</td>
</tr>
</tbody>
</table>

Results of the current study in regard to EHTN are supported by 2 preliminary case–control studies conducted by our group (preliminary odds ratios 2.73 and 3.03). All studies conducted by our group defined AC as present if a vessel was observed touching the ROS on the left and/or right side. The first preliminary study included a secondary analysis indicating significant association between AC of the ROS and EHTN on each side, considered separately.

The sidedness of AC in the ROS in EHTN is noteworthy in that early reports suggested that only left-sided compression was associated with hypertension. However, bilateral control of blood pressure has been seen in animal models; in humans, histochemical studies have shown C-1 neurons near the surface of the ROS on both sides. Although not the primary endpoint in a study by Hohenbleicher et al, it was reported that when brain stem contact was defined as vascular contact on the left, right, or both sides, this finding was more common in hypertensive than in normotensive patients (39% versus 25%, respectively; $P<0.05$). Interestingly, these percentages are similar to those found in our current study (42% versus 29%, respectively) even though the study populations are different (Hohenbleicher et al recruited hypertensive subjects from their hypertension clinic, normotensive subjects were genetically unrelated individuals identified through the patient or through newspaper announcements).

The location of vessel contact used in the current study was based on results from our ongoing studies aimed at mapping cardiovascular control functions along the VLM surface in humans. Mapping is achieved in these studies using bipolar electrode electrical stimulation of the ROS in consenting patients undergoing posterior fossa surgery for reasons other than hypertension. Preliminary results showed all stimulation responses to be significantly different from sham recordings (electrode placed/no stimulation), with repeat stimulations producing similar responses. A more recent mapping study suggests that an area can be localized on the VLM surface in the mid-ROS anterior to the nerve rootlets where stimulation produces an increase in mean arterial pressure. Areas mapped in the caudal ROS, both anterior and posterior to the nerve rootlets, respond with a marked decrease in mean arterial pressure and heart rate during stimulation. The mapping study so far suggests that the exact location of AC must be very clearly defined in future studies.

Strengths of this case–control study include the use of our mapping studies to define the area of compression and a uniform imaging technique with blinded review of images. Limitations include the inherent inability of the case–control design to adequately assess whether compression precedes and contributes to the development of hypertension, or
whether long-term hypertension leads to the development of arterial tortuosity and compression. A study by Naraghi et al showed that the rate of AC of the VLM was significantly lower in patients with renal hypertension than in patients with EHTN,30,31 suggesting that AC of the VLM is not caused by hypertension. Because the temporality of these events must be determined to support the argument for a causal relationship between pulsatile AC and EHTN, our group has proposed a prospective study to address this question.

Perspectives

If pulsatile AC in the ROS is found to have an etiologic role in EHTN, it would support the postulate for a treatable (with microvascular decompression) neural mechanism for the subgroup of subjects with essential hypertension who have chronic elevation of sympathetic tone and who do not respond to pharmacological therapy. Before advocating surgical treatment in this subgroup, additional questions remain to be answered. To this end, our future work will be directed specifically at establishing a refined map of the human ventrolateral medullary surface and its relationship to cardiovascular control. This map, along with imaging, will be used to identify eligible patients (intractable, with elevated sympathetic tone and AC in the relevant region of the ROS). In these patients, measures of sympathetic tone will be used to monitor changes in sympathetic activity immediately before and after microvascular decompression. If decompression can be shown to produce long-term reduction in blood pressure and/or hypertensive medications in these individuals, it could emerge as a viable treatment option for this subgroup of subjects with essential hypertension.

Acknowledgments

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References


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