Arterial hypertension and neurovascular compression at the ventrolateral medulla

A comparative microanatomical and pathological study

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Intraoperative observations and animal experiments suggest that neurovascular compression at the left ventrolateral medulla is a possible etiological factor in essential hypertension. In pursuing this hypothesis, the authors examined the neurovascular relations in the posterior cranial fossa of 24 patients with essential hypertension, of 10 with renal hypertension, and of 21 normotensive control patients. Artificial perfusion of the vessels and microsurgical investigations during autopsy identified the vascular relations at the brain stem and at the root entry zone of the caudal cranial nerves. There was no evidence of neurovascular compression at the ventrolateral medulla on the left side in any patient from the control group or among those with renal hypertension. Two normotensive patients had neurovascular compression at the right ventrolateral medulla by the posterior inferior cerebellar artery. In contrast, all patients with essential hypertension had definite neurovascular compression at the left ventrolateral medulla. Additional compression of the right side was seen in three of these patients. Based on the anatomical appearance, it was possible to define three distinct types of neurovascular compression at the ventrolateral medulla. Common to all three types is the compression of the medulla oblongata at its rostral part just caudal to the pontomedullary junction and lateral to the olive in the retro-olivary sulcus.

Comparative histopathological study of the microsurgically examined brain-stem specimens revealed no differences between patients with essential hypertension, those with renal hypertension, and normal controls. There was a structural integrity at the site of neurovascular compression at the ventrolateral medulla. The microanatomical findings of this study show that neurovascular relations at the ventrolateral medulla in essential hypertension give rise to pulsatile compression on the left. This supports Jannetta's hypothesis of neurovascular compression at the left ventrolateral medulla as an etiology of essential hypertension.

Key Words • neurovascular compression • arterial hypertension • root entry zone • ventrolateral medulla • C1 neuron • brain stem

After reports of Dandy\textsuperscript{18,19} and Gardner and Sava,\textsuperscript{26,27} Jannetta\textsuperscript{36–38} developed the concept of neurovascular compression as the etiology of hyperactive cranial nerve dysfunction syndromes. Pathological contacts between vessels and the root entry zones of cranial nerves close to the brain stem are regarded as causes of hyperactive cranial nerve dysfunction syndromes such as trigeminal neuralgia, hemifacial spasm, or glossopharyngeal neuralgia.\textsuperscript{1,3,36,38,45} Although this concept is still the subject of controversy, these entities are currently treated by surgical microvascular decompression with excellent results.\textsuperscript{1,18,27,41,46} In 1979, Jannetta and Gendel\textsuperscript{49} reported a possible etiological connection between essential hypertension and intraoperatively observed neurovascular compression of the ventrolateral medulla at the level of the root entry zone of the ninth and 10th cranial nerves on the left. Besides compression of the respective nerve, Jannetta and coworkers\textsuperscript{40,42} found an additional neurovascular compression at the left ventrolateral medulla in 51 patients with essential hypertension undergoing retromastoid craniectomy and exploration of the neurovascular relationship in the posterior cranial fossa because of hyperactive cranial nerve dysfunction syn-
dromes. Microvascular decompression of the ventrolateral medulla was performed in 42 patients with relief of hypertension in 36 of them; in six cases the procedure led to a reduction of antihypertensive medication. Further clinical studies support this suggestion. The influence of the central nervous system, sympathetic tone, and especially the medulla oblongata, on cardiovascular functions and blood pressure has been well known since 1873, when Dittmar observed a rapid fall in arterial blood pressure transsecting the brain stem at the pontomedullary junction. Porter separated the nervous control of the cardiovascular functions into a vasoreflex and a vasotonic control.

In an attempt to localize centers to which the reflex or tonic component could be attributed, Alexander explored the medulla oblongata by electrical stimulation. He described a lateral pressor area and a medial depressor area. Recent neurophysiological and neuroanatomical studies have demonstrated the importance of the ventrolateral medulla in the regulation of tonic cardiovascular reflexes. With immunohistochemical methods, Dahlström and Fuxe and Hökfelt and coworkers proved the existence of catecholamines in the brain stem. Catecholamine-containing neurons were named according to their content as A (noradrenaline), B (serotonin), or C (adrenaline), and numbered according to their location. Adrenaline-containing neurons at the rostral ventrolateral medulla, such as C1 neurons, seem to have an enormous tonic influence on the cardiovascular system.

Systematic pathoanatomical or clinical studies of the neurovascular relations at the brain stem in arterial hypertension as compared to the normotensive population have not yet been carried out. After observing neurovascular compression in two cases of essential hypertension with subsequent normalization of blood pressure following decompression of the left ventrolateral medulla, we initiated a comparative study consisting of a microanatomical study and a histopathological investigation. We considered that, if neurovascular compression at the ventrolateral medulla and the root entry zone of the ninth and 10th cranial nerves should be regarded as an etiology of arterial hypertension, it must be possible to demonstrate repeatedly such a finding in hypertensive patients without previous neurological condition. It was our goal to find and describe possible pathomorphological changes resulting from neurovascular compression and to correlate them to possible pathomechanisms of arterial hypertension.

Clinical Material and Methods

Case Selection

We examined at autopsy 55 patients treated at the Hannover Medical School who died at ages between 40 and 87 years (mean 69.3 years) (Table 1). Of those, 34 patients had a documented history of arterial hypertension: 24 were classified as essential hypertension and 10 as renal hypertension. In addition, we selected 21 individuals, aged 40 to 82 years, to serve as controls; these patients were known to have had normal blood pressure during life. None of the 55 patients examined had sustained permanent neurological deficits during life that would indicate possible long-lasting impairment of the central nervous system.

Patient histories, physical examination records, clinical charts, and autopsy reports were carefully reviewed. To fulfill the criteria for comparability, patients with arterial hypertension were matched to form three groups based on the duration of their elevated blood pressure. Clinically known hypertension had lasted up to 5 years in Category 1 patients, between 5 and 15 years in Category 2 patients, and more than 15 years in Category 3 patients (Table 1).

The cause of death in the 55 patients studied is summarized in Table 2. Acute ruptured aortic aneurysm was the most frequent cause of death in the group of patients with essential hypertension, followed by typical clinical complications of long-lasting arterial hypertension such as cardiovascular failure and myocardial infarction. Renal failure and multiple organic complications of chronic systemic diseases were the main fatal complications among the patients with renal hypertension. Primary causes of death among the control group included a range of neoplasias followed by infection and cardiovascular failure.

Microanatomical Studies

The anatomical studies were carried out 8 to 24 hours post mortem on specimens refrigerated at 4°C. The calvaria was removed carefully by means of a circular cut to avoid damage to the dura. Then the dura was opened and some cerebrospinal fluid was released. The adhesions of the hemispheres to the dura of the frontal cranial fossa were loosened and the tentorial notch was exposed. The cerebral peduncles were cut through transversely, and the hemispheres were removed from the skull, leaving the brain stem in situ under the tentorium in the posterior cranial fossa. The posterior cranial fossa was opened at the medial tentorial insertion in the petrous bone. Microsurgical technique (magnification × 6 to 25) was used to expose the ventral surface of the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group</th>
<th>Renal Hypertension</th>
<th>Essential Hypertension</th>
</tr>
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<tr>
<td>no. of cases</td>
<td>21</td>
<td>10</td>
<td>24</td>
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<tr>
<td>sex (M/F)</td>
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<td>4/6</td>
<td>15/9</td>
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<td>40-82</td>
<td>56-79</td>
<td>48-87</td>
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<tr>
<td>mean age (yrs)</td>
<td>63</td>
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<tr>
<td>duration of elevated blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 yrs</td>
<td>—</td>
<td>2 (0.2*)</td>
<td>4 (1.66†)</td>
</tr>
<tr>
<td>5-15 yrs</td>
<td>—</td>
<td>5 (0.5*)</td>
<td>13 (0.54†)</td>
</tr>
<tr>
<td>&gt; 15 yrs</td>
<td>—</td>
<td>3 (0.3*)</td>
<td>7 (0.29†)</td>
</tr>
</tbody>
</table>

* Relative frequency among 10 patients.
† Relative frequency among 24 patients.
Hypertension and neurovascular compression

<p>| TABLE 2 |
|----------------------|-----------------|------------------|------------------|
| Clinical causes of death in each group studied |</p>
<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Control Group</th>
<th>Renal Hypertension</th>
<th>Essential Hypertension</th>
<th>Total Cases</th>
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<tbody>
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<td>Central cardiovascular failure</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>11</td>
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<tr>
<td>Acute ruptured aortic aneurysm</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Spontaneous intracerebral hemorrhage</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>Pneumonia/sepsis</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Decompensated liver disease</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Multiple organic failure from chronic systemic disease</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>5</td>
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<tr>
<td>Complications of diabetes mellitus</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total cases</td>
<td>21</td>
<td>10</td>
<td>24</td>
<td>55</td>
</tr>
</tbody>
</table>

Brain stem by stepwise dissection along the clivus. The neurovascular relationships between the cranial nerves and vessels, especially at the root entry zone of the vagus and glossopharyngeal nerves and the ventrolateral medulla, were studied bilaterally.

Perfusion of the vessels in the posterior cranial fossa with an autologous blood-H₂O solution simulated the vital neurovascular status at the ventral surface of the brain stem. Cardiac ventricular blood diluted with water (1:1) retains an intense color for good photomicrographic contrast and does not change the brain parenchyma for the histological workup later. The blood solution was injected through a plastic catheter, which was introduced at the tip of the basilar artery or into the posterior cerebral artery. Bolus injections diluted the vessels for a short time and continuous perfusion, achieved with a pressure cuff (normally used for rapid forced infusion), achieved continuous dilatation. The cuff pressure was manometrically adjustable and a pressure range between 100 and 160 mm Hg was used. Neurovascular relations were studied with nonperfused and perfused vessels (including neurovascular compression). The findings were documented photomicrographically.

Finally, the brain stem was microsurgically removed, together with the cranial nerves and the vessels, and preserved in 10% formaldehyde solution for further histological studies.

Histological Studies

After the brain stems were removed from the posterior cranial fossa, the specimens were fixed for 14 days in 10% formaldehyde solution, following a macroscopic investigation in the Department of Neuropathology. The medulla was cut transversely into three equal discs from the pontomedullary junction over the length of the olive. The cut surfaces were vertical to the longitudinal axis of the brain stem. The root entry zone of the ninth and tenth cranial nerves, together with the rostral ventrolateral medulla, remained in the cranial disc, and caudal fibers of the vagus nerve and the medulla oblongata were in the intermedial portion; the caudal pole of the olive and the caudal medulla remained in the caudal part. After dehydration with ethanol solution, the specimens were embedded in paraffin and 2- to 5-μm serial cuts were obtained. We used the Masson trichrome and Klüver-Barrera staining techniques and examined the slides by light microscopy, seeking pathological changes such as cell degeneration, gliosis, fibrosis, swelling, demyelination, or hemorrhages.

In addition, the ventrolateral medulla and the root entry zone with the ninth and 10th cranial nerves were investigated separately in four patients who exhibited neurovascular compression with visible impressions on the root entry zones of the ninth and 10th cranial nerves. Two of these specimens were embedded in paraffin, cut along and across the fibers of the cranial nerves, and treated with Masson trichrome and Klüver-Barrera staining. The remaining specimens were prepared for semi-thin cuts after 24-hour treatment with glutaraldehyde, tripotassium phosphate buffer (pH 7.2), and 1% osmium tetroxide, and were then embedded in Araldite. The samples were cut along and across the nerve fibers; the slides were then stained with 2% toluidine blue and examined by light microscopy.

Results

Microanatomical Studies

Even in the face of great anatomical variations at the brain stem, we were always able to demonstrate a complete vascular tree in the posterior cranial fossa. The vertebral artery, basilar artery, posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery (AICA), and superior cerebellar artery were easily identified along with their origins. A dominant left vertebral artery was observed in 22 patients with hypertension and in 15 of the control cases.

None of the 21 normotensive cases had an abnormal neurovascular relationship at the ventrolateral medulla on the left. The root entry zones of the ninth and 10th cranial nerves and the ventrolateral medulla were clearly visible in all cases. All vessels that crossed the course of the nerves were distal to the root entry zone and had no attachment to the ventrolateral medulla. Compressing loops of the PICA were observed at the right ventrolateral medulla in only two cases (Fig. 1). No neurovascular compression at the left or right ventrolateral medulla was found in the 10 patients with renal hypertension.

In contrast, all 24 cases with essential hypertension displayed a definite neurovascular compression at the ventrolateral medulla on the left (Table 3). In three cases there was evidence of an additional neurovascular compression at the right ventrolateral medulla. In all 24, the medulla oblongata was compressed at the rostral portion just caudal to the pontomedullary junction, lateral to the olive in the retro-olivary sulcus. The compressing vessel coursed with a convex loop pointing toward the medullary parenchyma in a craniocaudal direction, vertically to the fibers of the ninth and 10th

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cranial nerves, and encompassing the complete extent of the medial surface of the root entry zone (Figs. 2, 3, and 4).

Altogether, we observed 29 instances of neurovascular compression at the ventrolateral medulla. The compression appeared 24 times on the left side and five times on the right side (Table 4). The PICA caused neurovascular compression at the left ventrolateral medulla alone in 14 cases and combined with the vertebral artery in five cases. The vertebral artery alone was compressive in three instances. Compression by the basilar artery and the AICA was observed once each. At the site of compression in our 29 instances, the diameter of the offending vessels ranged from 2 to 7 mm (mean 3.4 mm), with two peaks of incidence: one at 2 mm and the other at 6 mm (Fig. 5). The length of the compressed area was always equal to that of the cranio-caudal extension of the root entry zone of the vagus and glossopharyngeal nerves (Figs. 2 and 4).

We could find no venous compression at the ventrolateral medulla in this postmortem series. The identification of neurovascular compression, especially of the ventrolateral medulla with perfused vessels, was very easy. There was also no problem in identifying neuro-

### TABLE 3

Findings of neurovascular compression (NVC) in 55 autopsy studies

<table>
<thead>
<tr>
<th>Factor</th>
<th>Control Group</th>
<th>Renal Hypertension</th>
<th>Essential Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>21</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>rt unilat NVC</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>lt unilat NVC</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>bilat NVC</td>
<td>0</td>
<td>0</td>
<td>3*</td>
</tr>
<tr>
<td>total NVCs</td>
<td>2</td>
<td>0</td>
<td>27</td>
</tr>
</tbody>
</table>

* Three bilateral cases = six instances of NVC.

### TABLE 4

Arteries causing neurovascular compression in 55 autopsy studies

<table>
<thead>
<tr>
<th>Artery</th>
<th>No. of Cases</th>
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<tbody>
<tr>
<td>basilar</td>
<td>1</td>
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<tr>
<td>vertebral</td>
<td>3</td>
</tr>
<tr>
<td>anterior inferior cerebellar</td>
<td>1</td>
</tr>
<tr>
<td>posterior inferior cerebellar</td>
<td>14</td>
</tr>
<tr>
<td>vertebral &amp; posterior inferior cerebellar</td>
<td>5*</td>
</tr>
<tr>
<td>veins</td>
<td>0</td>
</tr>
<tr>
<td>no. of vessels</td>
<td>29</td>
</tr>
</tbody>
</table>

* Each case had two simultaneously compressing vessels.
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vascular compression when the vertebral artery was involved or if sclerotic walls prevented the vessel from collapsing. Collapsed vessels were attached to the root entry zone in neurovascular compression; in this condition, the convexity pointing toward the medulla along the course of the vessels was recognizable. Perfusion erected the collapsed vessels and the compression of the medulla then became apparent, indicating pulsatile compression at this site.

Histological Results

We were able to obtain serial cuts from all examined cases. Comparative light microscopic study of the slides showed no difference between the groups with arterial hypertension and the control cases. The precise point of compression at the ventrolateral medulla could not be determined by distinct pathological changes. In rostral cuts, the reticular formation extended its fiber network and neurons to the ventrolateral surface, where the neurovascular compression was seen on anatomical examination. The central structures of the reticular formation were symmetrical. There we found medium-sized multipolar neurons scattered diffusely in the network (Fig. 6).

Impression and dense aggregation of the nerve fibers at the junctional zone were evidence of neurovascular compression in six cases. Pressure-induced degeneration of nerve fibers or demyelination could not be detected in the semi-thin cuts (Figs. 7 and 8).

Discussion

Literature Review

Our consistent finding of a close connection between essential hypertension and neurovascular compression at the ventrolateral medulla on the left side corresponds to intraoperative observations by Jannetta, et al. They reported neurovascular compression at the ventrolateral medulla in 51 of 53 patients with essential hypertension undergoing retromastoid craniectomy for hyperactive cranial nerve dysfunction syndromes such as trigeminal neuralgia, hemifacial spasm, or glossopharyngeal neu-
ralgia. In their surgically treated cases, they saw neurovascular compression only on the left ventrolateral medulla. Because intraoperative observation does not allow examination on both sides, Jannetta, et al., could not comment on neurovascular compression of the ventrolateral medulla on the nonoperative side; however, they tried to verify the hypothesis on the basis of findings during right-sided retrosigmoid craniectomy. We found no neurological signs of cranial nerve dysfunction in our group of patients with hypertension.

The compression at the ventrolateral medulla that existed in addition to neurovascular compression of the trigeminal or facial nerve, as observed by Jannetta, et al., was not to be attributed to trigeminal neuralgia or hemifacial spasm, but to essential hypertension.

Several anatomical and microanatomical studies of neurovascular relationships have been carried out. Watt and McKillop were the first to report finding signs of neurovascular compression at autopsies. A review of the 1948 study by Sunderland even reveals signs of the vertebral type neurovascular compression on the left side in one of the published photographs. Microsurgical analyses by Rhoton and coworkers and Fein also point in this direction. Fein found a close anatomical relationship between the course of the ninth and tenth cranial nerves and the PICA on the left side in seven of eight patients with primary hypertension, but he did not describe the vascular relationship to the ventrolateral medulla and the root entry zone. However, because of the irregular vascular pattern along the course of the caudal cranial nerves, he also assumed that compression of the medulla must be the causative factor. Fein's study was mostly performed on excorparated fixed specimens, so one may assume some difficulties in describing neurovascular compression.

With the artificial perfusion used in our study, it is possible to obtain an almost vital picture of the anatomical relationships. Pressure-induced dilatation of the vessels makes it possible to judge the neurovascular relationships easily. Hypertension itself leads to changes and may result in ectasia and elongation of the cerebral vessels. If such neurovascular contacts as we observed were the result and not the cause of hypertension, one would expect to find neurovascular compression with the same frequency on both sides of the brain stem. One would also expect to find an increased vascular looping of brain-stem vessels with neurovascular compression of the third through seventh cranial nerves, which should cause other forms of hyperactive cranial nerve dysfunction syndromes besides hypertension. This seems to be refuted by the autopsy findings in patients with renal hypertension, the most common form of secondary hypertension. In our autopsy specimens, we found no compressing vascular loop at the upper brain stem.

Fig. 6. Photomicrograph of histological specimen from the rostral medulla oblongata with the compressing vessel (A) at the left ventrolateral medulla (VLM), which distorts the root entry zone (REZ) of the vagus nerve. C = area of the C, neurons; FR = reticular formation; O = olive; 10 = vagus nerve. Klüver-Barrera stain, × 25.

Fig. 7. Photomicrographs demonstrating histology of a compressed nerve, a longitudinal section (left) and a cross section with the wall of the compressing artery (right). AW = arterial wall; M = medulla; N10 = vagus nerve; P = peripheral nerve; REZ 10 = root entry zone of the 10th cranial nerve; UZ = junctional zone; Z = central zone. Paraffin-embedded specimens. Klüver-Barrera (left) and Masson trichrome (right), × 135.
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Trigeminal Neuralgia and Hemifacial Spasm

There are no clinical data indicating a high incidence of trigeminal neuralgia or hemifacial spasm in cases of arterial hypertension. The overall occurrence of essential hypertension in a population of 226 patients with hyperactive cranial nerve dysfunction syndromes was comparable to and did not show any significant difference from that of a reference population. This was proven in 1988 in a clinical study by van Ouwerkerk, et al. In the same study they found evidence for the existence of a subgroup of patients with left-sided hemifacial spasm who have a higher prevalence of essential hypertension. Because of the proximity of the seventh, ninth, and tenth cranial nerves to the ventrolateral medulla, van Ouwerkerk, et al., suspected that changes of the vertebral artery and its branches, leading to compression of the facial nerve, are predisposing factors for neurovascular compression developing at the ventrolateral medulla, which has an etiological connection to essential hypertension.

Types of Neurovascular Compression in Essential Hypertension

Comparison of the anatomical pattern of neurovascular compression at the ventrolateral medulla in essential hypertension with that of the trigeminal or facial nerve reveals distinct differences. The compressed area always extends along the root entry zone of two cranial nerves and covers a relatively large area on the surface of the medulla. In trigeminal neuralgia or hemifacial spasm, vessels ranging from 0.3 to 2 mm cause neurovascular compression; however, in this study we observed only vessels with a large caliber effecting neurovascular compression at the ventrolateral medulla (Fig. 5).

Based on our findings and the course of the vessels at the ventral surface of the brain stem, we were able to define three distinct types of neurovascular compression at the ventrolateral medulla (Fig. 9): Type I (monovascular), in which compression is caused by a single vessel loop that is the main branch of a vessel originating from the vertebral or basilar artery (the PICA is the most frequent offending artery in this type); Type II (vertebral), in which compression is caused by an elongated ectatic vertebral artery; and Type III (combined), in which the vertebral and PICA's together cause compression. In our study, we found 15 instances of Type I, four of Type II, and five of Type III compression.

Histological Studies

The results of our histological studies confirm that neurovascular compression does not lead to any pathomorphological changes detectable by light microscopic methods. We presume that the pressure impulse is not very intense and just leads to local irritation of the comprised neural structures, as described by Sunderland. This irritation would simply change the functional level. Jannetta, et al., however, found electron microscopic evidence of myelin degeneration in nerve biopsies obtained from surgery, but this has not yet been confirmed. Because our study was performed on

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Fig. 8. Photomicrographs showing semi-thin cuts of a compressed nerve demonstrating intact myelin in the longitudinal (left) and transverse (right) sections. NF = nerve fiber. Araldite-embedded sections. Toluidine blue. x 535.

Fig. 9. Diagram showing three types of neurovascular compression at the left ventrolateral medulla in essential hypertension. Type 1 is monovascular, Type 2 is vertebral, and Type 3 is combined. For further description see text. n = number of instances in this study.
autopsy specimens, electron microscopic studies would lead to unreliable results and it would be difficult to differentiate between postmortem artifacts and possible degeneration of nerve fibers and myelin caused by neurovascular compression.

The question of the consequences of additional right-sided neurovascular compression in essential hypertension is still open. Neither Jannetta, et al., nor other authors have commented on this connection. Why right-sided compression is observed much less frequently and whether there is any clinical significance to this location is unclear.

Pathophysiology of Neurogenic (Essential) Hypertension: Hypothesis

The significance of the structural integrity of the rostral medulla oblongata for maintenance of cardiovascular function and blood pressure was shown by Dittmar in 1873. He transected the brain stem in rabbits stepwise from cranial to caudal and noticed a rapid fall in blood pressure at the pontomedullary junction. The epinephrine-synthesizing C1 neurons of the reticular formation, which were demonstrated by Hölzel, et al., in 1974, are localized at this level close to the ventrolateral surface of the medulla. Because of their location, Ross, et al., designated this group of cells as the "nucleus rostralis ventrolateralis."

Recent results from different studies on several species of animals revealed the tonic control of the cardiovascular functions by C1 neurons of the ventrolateral medulla. Electrical and chemical stimulation of these cells results in elevation of arterial blood pressure. Glutamate, known as an excitatory neurotransmitter which stimulates the cell bodies, induces a long-lasting rise in arterial pressure after local microinjection into the C1 area. In contrast to this, application of inhibitory substances (such as gamma-aminobutyric acid (GABA), tetrodotoxin, or glycine) or local destruction and cooling of this area reduces the blood pressure. Bilateral elimination of the C1 neurons results in a fall in blood pressure, as is observed during spinal shock, with a high transverse lesion of the spinal cord.

Amendt, et al., described in 1979 the efferent connections of the C1 neurons in the rostral ventrolateral medulla to the preganglionic sympathetic neurons of the intermediolateral column in the thoracic spinal cord by means of the uptake and retrograde transport of horseradish peroxidase. This was confirmed by many other studies. By this connection, the C1 neurons have a direct excitatory control over the sympathetic nervous system, resulting in elevation of the plasma catecholamine level and elevated discharge of peripheral sympathetic fibers. By the same method, efferent connections of the C1 neurons to the paraventricular nucleus of the hypothalamus were described with consecutive elevation of plasma vasopressin after stimulation.

Afferent fibers reach the C1 neurons from different areas of the central nervous system. Well to the fore here is the ipsilateral nucleus tractus solitarii to which the C1 neurons are reciprocally connected and from which they receive inhibitory GABA-ergic fibers. The nucleus tractus solitarii is the primary site for processing the affere-nces from the baroreceptor reflex and the myocardial vagal c-fibers. Granata, et al., studied the role of the C1 neurons in the processing of the baroreflex arch and the phasic regulation of cardiovascular functions in addition to their tonic influence. This response is completely abolished when the C1 area is lesioned contralaterally to a previously destroyed nucleus tractus solitarii, so that no input reaches the C1 cells on either side, despite one remaining intact nucleus tractus solitarii and one remaining intact contralateral C1 area.

Just caudal to the C1 neurons are norepinephrine-synthesizing A1 neurons, which are also connected to the nucleus tractus solitarii and have a depressor effect after stimulation. Goodchild, et al., and Blessing and coworkers explained the concomitant rise in blood pressure after lesioning the A1 neurons by an increase in the pressor effect of the C1 neurons. In many of their experimental animals, the acute excessive stress to the cardiovascular system led to acute pulmonary edema and cardiovascular failure.

It seems that neurovascular compression at the ventrolateral medulla leads to a permanent irritation and activation of the C1 neurons. The studies cited do not show any evidence for a left-sided dominance in the regulation of cardiovascular functions. A possible explanation for the left neurovascular compression in essential hypertension is the additional compression of the root entry zone of the ninth and tenth cranial nerves. The major part of the afferent inputs from the myocardial receptors of the left ventricle and atrium to the nucleus tractus solitarii are conducted by the low-myelinated cardiac c-fibers of the left vagus nerve. One may guess that conduction is partially blocked in these vulnerable fibers by neurovascular compression and, as a result, the nucleus tractus solitarii undergoes partial deafferentation. In animal experiments, complete deafferentation or destruction of the nucleus tractus solitarii results first in a fulminant hypertension, which gradually changes into a chronic labile blood pressure.

Jannetta and coworkers induced a rise in blood pressure with a neurovascular simulator in the so-called "balloon-balloon model" in baboons. As soon as the system was inflated, the animals' blood pressure began to rise, and it fell again when the balloon was deflated. This study points to the importance of pulsatile compression applied to the medulla. Reversion of a pre-existing hypertension after microsurgical decompression of the ventrolateral medulla, as reported by Jannetta and coworkers, and Naraghi, et al., is clinical evidence for the structural integrity of the ventrolateral medulla in neurovascular compression. Although van Ouwerkerk, et al., found a recurrence of hypertension in more than 50% of the decompressed cases, all of these authors reported a reduction in blood pressure for...
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a significant period of time following surgical manipulation at the ventrolateral medulla on the left. None of the existing studies gives any data about the immediate postoperative course of blood pressure and when the normalization appears. Although we observed an early drop following decompression of the ventrolateral medulla, there remained a significant lability of blood pressure for the next 2 to 3 weeks in our two cases.48 At the 12-month follow-up examination this lability had disappeared and our patients remained normotensive.

Further clinical evidence of an association between essential hypertension and neurovascular compression of the ventrolateral medulla is offered by retrospective evaluation of vertebral angiograms. Kleinberg, et al.,49 found convex arterial loops in close proximity to the left ventrolateral medulla in about 80% of angiograms obtained from hypertensive patients.

Conclusions

The results of our studies, together with the present knowledge, indicate a central role of the ventrolateral medulla in the processing and control of cardiovascular functions. There is additional evidence for an etiological connection between neurovascular compression at this site and essential hypertension. Controlled prospective clinical and experimental studies seem to be justified to further clarify this hypothesis and to find possible clinical indications for microvascular decompression as a treatment modality for arterial hypertension.

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