Views and Perspectives

The Extracranial Vascular Theory of Migraine—A Great Story Confirmed by the Facts

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Over the years, there has been a considerable amount of controversy as to whether the vascular component of migraine pain arises from the intracranial or the extracranial vessels or both. Some have even questioned whether vasodilatation even plays a significant role in migraine pain and have described it as an unimportant epiphenomenon. In this review, evidence is presented that confirms (1) vasodilatation is indeed a source of pain in migraine; (2) this dilatation does not involve the intracranial vasculature; (3) the extracranial terminal branches of the external carotid artery are a significant source of pain in migraine.

Key words: migraine, extracranial artery, migraine pain

Following the work of Leaõ[1] on cortical spreading depression (CSD) and Sicuteri's work with serotonin,[2] the major focus of headache research shifted almost exclusively to the intracranial structures and centrally located pathophysiological changes. Since then, some of the extracranial peripheral links in the complex chain of events that occur in migraine have largely been ignored and forgotten.

Great strides have been made in understanding certain of the changes that occur during the course of a migraine attack, such as central sensitization,[3-6] peripheral sensitization,[7-12] cutaneous allodynia,[4,13-16] and the influence of genetic factors.[17,18] However, our understanding of migraine has been hampered because a major element, the role of the extracranial terminal branches of the external carotid artery, inexplicably has been relegated to the sidelines in recent years.

Harold Wolff and his co-workers were the first to subject the phenomenon of vasodilation to rigorous scientific testing. Wolff's vascular theory of migraine consisted of 2 elements: (1) that intracranial vasospasm of the cerebral arteries causes the aura of migraine, and (2) that extracranial vasodilatation (together with lowered pain threshold, concurrent intramural vascular edema, and local sterile inflammation) is a cause of migraine pain.[16,19,20]

Wolff's theory held sway for about 30 years, until Olesen and the "Copenhagen Group" were able to demonstrate by measuring regional cerebral blood flow during migraine aura that the pattern of spread of oligemia (and, presumably, CSD) did not conform to the anatomical boundaries of the major cerebral blood vessels.[21] This was felt to indicate that cerebral artery vasospasm could not account for CSD, and the first part of Wolff's theory was correctly discredited.

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As Olesen's study was not conducted on the extracranial vessels, it had no relevance to—and consequently neither contradicted nor discredited—the second part of Wolff's theory.

It is only this latter portion of Wolff's theory that is discussed in this review, and the wealth of evidence to be presented serves strongly to suggest that not only does vasodilatation play a role in migraine pain, but that this dilatation is extracranial and not intracranial. Wolff did not merely theorize on the role of dilatation of these vessels in migraine; he confirmed his theory with a series of elegant and meticulously executed experiments, the results of which have never been successfully challenged.

Such attempts as have been made to repudiate Wolff's theory have been based on evidence that is irrelevant with regard to the extracranial arteries. One such instance is the investigation by Olesen et al, wherein evidence was provided that the painful phase of migraine did not correlate with intracranial vasodilatation, a study that has been cited on more than one occasion in the attempt to disprove Wolff's theory.[22-27] What Wolff's detractors omitted to mention, however, is that Olesen's research involved regional cerebral blood flow and had nothing to do with the extracranial arteries or blood flow (Fig. 1).
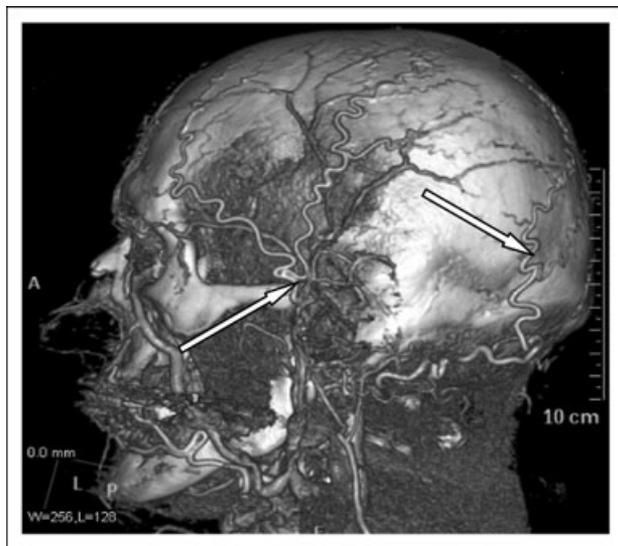

Fig 1.—Computed tomography angiogram showing the superficial temporal and occipital arteries which form the basis of Wolff's theory of extracranial vascular pain.

INTRACRANIAL VASODILATATION AND MIGRAINE PAIN

A landmark article by Schoonman et al showed conclusively that intracranial vasodilatation is not related to the painful phase of migraine.[28] These investigators were able for the first time to directly and accurately measure the diameters of most of the major intracranial and some of the extracranial vessels, both during migraine and interictally, on left and right sides, during unilateral migraine. They found that none of the vessels measured appeared to dilate during the migraine attack.[28] Clearly contradicting the widely held notion that dilated intracranial arteries, as part of the trigeminovascular system (TVS), were the source of pain in migraine, the authors concluded that "In contrast to widespread belief, migraine attacks are not associated with vasodilatation of the cerebral or meningeal blood vessels." Their investigation of the meningeal vessels, however, was not altogether complete, as they did not study the intracranial (dural) portion of the middle meningeal artery, a vessel that has been implicated as the primary vascular component of the TVS. Even so, subsequent anatomical studies have shown that this segment of the human middle meningeal artery is prevented from dilating by virtue of its being encased in the tough, inelastic, and unyielding collagenous dura.[29] Although Schoonman et al studied the terminal 1 cm of the external carotid artery before its bifurcation (Fig. 2), they measured neither the superficial temporal artery nor the occipital artery, which were central to Wolff's theory (Fig. 1).

Although Schoonman et al were the first to directly measure arterial diameters during migraine, there has long existed convincing experimental and anatomical evidence that the intracranial vasculature is not the source of migraine pain. The first experimental evidence was provided 70 years ago by Schumacher and Wolff, who showed by comparing the effects of raised intracranial pressure on histamine headache and migraine headache that intracranial vasodilatation is unlikely to be the source of pain in migraine.[19] They reasoned that by virtue of their location within the unyielding skull, the intracranial arteries could be compressed by increases in cere-
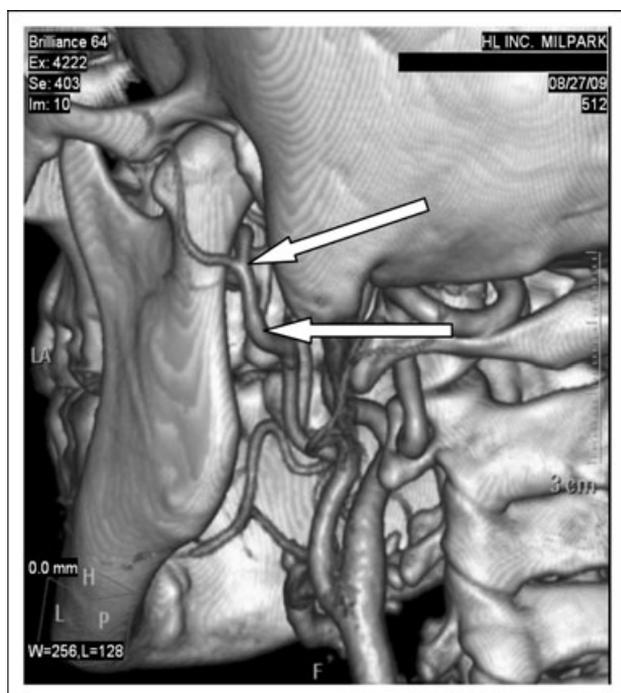
Fig 2.—The 1 cm section of the external carotid that Schoonman et al[25] measured, proximal to its bifurcation into its maxillary and superficial temporal terminal branches.

brospinal fluid (CSF) pressure. In a headache resulting from dilation of intracranial arteries, they concluded the increased intracranial pressure caused by raising the CSF pressure would result in diminished amplitude of pulsation waves and pain reduction. Conversely, if no reduction in pain intensity occurred, it would indicate that the pain was not intracranial in origin. They devised a method of rapidly increasing CSF pressure by connecting the subarachnoid space to a column of sterile physiologic saline; the column could be raised or lowered to increase or decrease CSF pressure.

It previously had been established that dilated intracerebral arteries were the origin of pain in histamine-induced headache.[30] As a control group, non-migraineurs with histamine-induced headache were used, and in the 11 subjects with histamine-induced headache, their head pain was relieved within 15 to 90 seconds of raising the intracranial pressure to an average of 350 mm H_2O. These same subjects invariably experienced a recurrence of pain following rapid reduction of CSF pressure.[19] In 6 out of the 7 subjects with migraine headache, however, no

change in pain intensity occurred even when the CSF pressure was increased to as high as 700 to 1000 mm H_2O for up to 30 minutes. The authors concluded that: (1) the pain of histamine-induced headache originates from dilatation of the intracranial vessels; and (2) the pain of migraine headache does not originate from dilatation of those vessels.[19]

Using functional neuroimaging techniques, investigators reliably have shown that during migraine there is a prolonged period of cerebral hyperperfusion.[21,31,32] If the headache of migraine were related to dilation of cerebral arteries, then it could be reasonably expected that the pain would coincide with this hyperperfusion; but Olesen and the "Copenhagen Group" demonstrated that the cerebral hyperperfusion observed to occur in migraine is unrelated to the severity and timing of migraine pain.[21]

EVIDENCE SUPPORTING WOLFF'S THEORY THAT THE EXTRACRANIAL VASCULATURE IS A SOURCE OF PAIN IN MIGRAINE

The evidence confirming that migraine pain arises from the superficial terminal branches of the external carotid artery is as follows:

1. Experimental
2. Physiological
3. Pharmacological
4. Clinical

Experimental Evidence.—*Pulsation Amplitude.*— A comparison of the mean pulse amplitude of the frontal branch of the superficial temporal artery of 10 control subjects with that of 10 migraineurs examined interictally showed that the mean pulse amplitude in the migraineurs—even in the absence of headache—was twice that of the control subjects.[33] Wolff and his co-workers also demonstrated that changes in the intensity of migraine headache were closely related to changes in the amplitude of pulsations in the occipital and superficial temporal branches of the external carotid arteries; factors that decreased the amplitude of pulsations decreased the intensity of headache and vice versa.[34,35] When the intensity of the pain diminished rapidly, the ampli-

tude of pulsations likewise diminished rapidly. When the intensity of the headache diminished slowly, the pulsations decreased slowly.[36] These finding were confirmed by Brazil and Friedman.[37]

Luminal Diameter.—Although it was suggested that the increase in pulse amplitude merely may have reflected thickening of the arterial walls because of intramural edema, it was later confirmed by Iversen et al that the luminal diameter of the involved vessels does indeed increase during migraine.[38,39] Those investigators used high-resolution ultrasound to measure the luminal diameters of the frontal branches of the superficial temporal arteries in 25 female migraine patients with unilateral migraine (22 without aura and 3 with aura). The arteries were measured during headache on the ipsilateral and contralateral sides and also when the patients had been headache-free for 7 days. During migraine attacks, the median luminal diameter of the frontal branch of the superficial temporal artery on the affected side was greater than that on the non-painful side.[39]

Extracranial Blood Flow.—Elkind et al used the tissue clearance method of Na^{24} to measure frontotemporal blood flow in 72 patients with "vascular headaches of the migraine type" and in 10 control subjects.[40] In the absence of headache, the difference in blood flow between migraineurs and controls was not significant. During headache, however, blood flow on the painful side was significantly increased over that of either asymptomatic patients or control subjects ($P < .005$). In addition, during unilateral headache, blood flow was higher on the painful side than on the contralateral side ($P < .01$). In 7 patients with severe headache, investigators measured frontotemporal skin blood flow before and after the administration of ergotamine tartrate.[40] In 5, the headache disappeared within 30 minutes, with a corresponding reduction in blood flow. In the 2 patients who did not respond to ergotamine, frontotemporal blood flow remained elevated. Similar results were obtained using norepinephrine as the vasoconstrictor; of 6 patients given norepinephrine, 5 responded with "prompt reduction of frontotemporal skin blood flow with simultaneous improvement of headache," and in the remaining patient, blood flow increased concomitant with an increase in pain inten-

sity. The authors concluded that the high correlation between reduction of blood flow and amelioration of headache following administration of a vasoconstrictor suggested that the pain was related to local vascular changes. These findings were later confirmed in a study involving 18 patients with migraine with aura and 37 patients with migraine without aura via the ^{133}Xe inhalation method.[41,42]

Physiological Evidence.—*Calcitonin gene-related peptide (CGRP).*—If the effect of CGRP in migraine is because of its action as a powerful vasodilator, but, as has been indicated, the intracranial arteries do not dilate during migraine, then what vessels does CGRP dilate? The only other arteries in the region are extracranial, and there is compelling evidence that CGRP site of action in migraine is the extracranial vasculature. The evidence is as follows:

1. CGRP is found in the walls of the superficial temporal arteries.[43]
2. CGRP is a potent vasodilator of human superficial temporal arteries.[43,44]
3. Two studies have shown a substantial elevation of CGRP levels in external jugular venous blood during acute migraine both with and without aura[44,45] (as a third study could not confirm this finding in migraine without aura, there remains some uncertainty as to whether CGRP is increased in the external jugular venous blood of all migraineurs[46]). Although some external jugular blood originates intracranially (about 20%), this is too little to account for the recorded increase in external jugular CGRP.[47] Thus, changes in the levels of CGRP found in the external jugular vein perforce reflect changes in the extracranial tissue that it drains.
4. Relief of migraine pain by triptan administration coincides with reduction and normalization of CGRP levels in the extracranial blood.[48,49] The same phenomenon occurs following triptan administration in nitroglycerine-induced migraine attacks.[50]

Pharmacological Evidence.—*Migraine Rescue Medications.*—The most effective migraine rescue medications are the ergots (ergotamine tartrate and

dihydroergotamine [DHE]) and the triptans, and both are potent vasoconstrictors of the extracranial vessels.[20,51] A new class of drugs which seem likely to be important in migraine treatment, the gepants, have no vasoactive effect on normal arteries but potently reverse the abnormal CRGP-induced dilatation of the extracranial vessels.[52] Impossible to ignore, then, is the fact that the single property shared by the most widely used anti-migraine preparations—past, present, and (potentially) future—is their potent constriction of abnormally dilated extracranial arteries, simultaneously accompanied by the reduction or elimination of migraine pain. Also pertinent, to date all migraine-provoking agents have had vasodilating properties.[53]

Ergots.—Ergotamine tartrate has been used for acute migraine treatment for approximately 80 years.[36] In therapeutic doses it is a vasoconstrictor, and the drug potently constricts the terminal branches of the external carotid artery.[54,55] DHE is also a potent constrictor of the extracerebral arteries in humans.[36,54] Brazil and Friedman were able to demonstrate that after DHE administration there exists the same relationship between headache intensity and pulsation amplitude, as Wolff and Graham found after administration of ergotamine tartrate.[37]

Although ergotamine has a long-lasting vasoconstrictor activity mainly in the vascular region supplied by the external carotid artery, it does not affect cerebral blood flow even when effective in abolishing migraine headache.[21,22,56] The conclusion that the therapeutic effect of ergotamine depends on its ability to produce extracranial vasoconstriction led to experimentation with other vasoconstrictors, and administration of ergonovine, caffeine, benzedrine, ephedrine, and pitressin all resulted in reduction of migraine headache commensurate with a reduction in the pulsation amplitude of the superficial temporal artery.[10]

Triptans.—This class of drugs was designed to selectively constrict intracranial blood vessels, but 3T magnetic resonance imaging and anatomical studies now have provided conclusive evidence that migraine headache is not associated with dilatation of the intracranial blood vessels.[28,29,57] Although sumatriptan may not produce any beneficial vasoconstrictive

action via the intracranial vessels, it is a potent constrictor of human temporal arteries.[51] Furthermore, when migraine pain is relieved by triptan administration, there is a concomitant reduction in CGRP levels in the extracranial blood.[48-50]

Gepants.—The first of the gepants, BIBN4096BS, was developed specifically to reverse the vasodilatation caused by the increased CGRP levels during migraine.[58] In an international, multicenter, double-blind, randomized clinical trial of BIBN4096BS involving 126 patients, the drug was effective in treating migraine and was significantly superior to placebo ($P = .001$).[59] Although it has the desirable quality of having no vasoactive effect on normal arteries, it is a powerful constrictor of dilated migrainous arteries and completely inhibits CGRP-induced dilatation of the superficial temporal artery.[52,55,60]

Clinical Evidence.—*Extracranial Arterial Compression.*—Compression of the extracranial arteries affords pain relief to some migraineurs; digital compression of one or more of the extracranial arteries—in particular, the superficial temporal and occipital arteries—reduces or eliminates migraine pain.[61-63] In one study, vigorous bilateral compression and massage of the frontal branches of the superficial temporal artery during the aura phase was successful in preventing headache in 34 of 42 attacks, and the application of a tight head band affords relief in some cases.[62,64-66] In a cohort of 35 migraineurs, the application during headache of an inflatable head cuff to a pressure of 10 mmHg below the systolic pressure resulted in pain relief in 71% of patients, increased pain intensity in 6%, and produced no change in 23%.[67] When the cuff inflation was increased to 10 mmHg above the systolic pressure, only 47% experienced pain relief, whereas in 18% the pain was worse, and 35% experienced no change. A possible explanation for this discrepancy is that pain is caused by the higher pressure exerted upon scalp tissues afflicted by neurogenic inflammation, tender edematous arterial walls, and tender underlying pericranial muscles.[16,68-70]

Biofeedback Regulation.—Biofeedback-associated self-regulation of the superficial temporal artery is effective in reducing both the frequency and the intensity of migraine.[71,72] Clinically meaningful head-

ache reductions can be achieved and maintained consequent to this form of biofeedback.

DISCUSSION

To date, the hypothesis that intracranial vasodilatation is a source of migraine pain has not been supported by existing evidence. This does not exclude the possibility that the intracranial vasculature may be a source of pain in some migraineurs, but until such time as confirmatory evidence is available, this remains an unproven hypothesis.

Conversely, there is a great deal of verifiable and unrefuted experimental, physiological, pharmacological, and clinical evidence to support Wolff's proposal that extracranial vasodilatation is a source of pain in migraine, albeit accompanied by lowered pain threshold, concurrent intramural vascular edema, and local sterile inflammation.[15,16,19,20,30,34-36,39-45,48-54,60-67,71-81] Wolff's theory has stood the test of time.

Despite this, there is a reluctance on the part of many headache specialists to accept that Wolff's theory possesses any validity, and that reluctance has resulted in the exclusion of Wolff's vascular theory from the suggested curricula for American medical students.[23,24,62,82,83] Also of concern is that all mention of Wolff's theory has been expunged from later editions of his own book, the widely read *Wolff's Headache and Other Head Pain*.[84] Readers wishing to glean more information about Wolff's work are advised to consult earlier editions of his book; the third edition contains detailed descriptions of his ground-breaking research.[20]

SUMMARY

That vasodilatation is an important factor in migraine is demonstrated by the fact that the most widely used migraine rescue medications, the ergots and the triptans, and the most promising of the newer drugs, the gepants, possess one significant common denominator: they all potently constrict abnormally dilated extracranial arteries while simultaneously reducing or eliminating migraine pain. Furthermore, to date all migraine-provoking agents have had vasodilating properties.

It is important to emphasize that Wolff did not suggest vasodilatation *caused* migraine. Nor did he suggest that extracranial vasodilatation necessarily could produce migraine pain without concomitant neurogenic inflammation, intramural edema, and a lowered pain threshold. Nor did he claim that extracranial vasodilatation was the *only* source of migraine pain. There is, however, an abundance of compelling physiological, experimental, pharmacological, and clinical evidence to indicate that in many migraine sufferers their pain originates in the dilated extracranial terminal branches of the external carotid artery.

Wolff's extracranial vascular theory of migraine is scientifically sound; it is testable, and it has been confirmed, repeatedly, by fact. While it's unlikely that Wolff's theory soon will be accepted by its opponents, eventually the evidence must prevail. As J.B.S. Haldane said, "Theories have four stages of acceptance: (1) this is worthless nonsense; (2) this is an interesting, but perverse, point of view, (3) this is true, but quite unimportant; (4) I always said so."

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