## MICROCIRCULATION PATHOPHYSIOLOGY IN CHRONIC REGIONAL PAIN SYNDROMES

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Chronic Pain Syndromes, migraine and CRPS/ RSD both have the following similarities:

1) a chronic pain state with associated allodynia and hyper- pathia (1,2,3)

2) regional perfusion abnormalities (4,5)

3) neuropeptide changes, e.g., CGRP (6,7)
4) A-V $O^2$ difference (8,9) or tissue hypoxia (10,11) and

5) role of AVAs in altering flow independent of metabolism (12,13).

The microcirculatory alterations resulting in regional neuropeptide sensitive perfusion changes can manifest as altered A V $O^2$ difference (8,9) or as tissue hypoxia (10,11). The release of vasoactive peptides from a remote site can also induce prolonged changes in vasomotion of the AVAs (14).

The role of AVAs in migraine pathophysiology was published by Heyck in 1956 (8).

The mechanism of action of antimgraine drugs have been studied with reference to its effect on AVAs by Johnston and Saxena in 1978 (9) and Spierings and Saxena in 1979 (15). The methodology and clinical implications of imaging microcirculatory vasomotor changes due to AVAs in migraine has been published (16,17). Thermography can image microcirculatory vasomotor changes due to arteriov enous anatamoses ( AVAs) and has diagnostic and prognostic significance in chronic pain syndromes like migraine and CRPS/RSD. Drs. Swerdlow and Dalla Volta have focused on its relevance to migraine diagnosis , management and clinical course (18,19). In the diagnosis of CRPS /RSD (20, 21) baseline temperature asymmetry or stress infrared telethermography has been documented to be useful.

During the last few years, there has been increasing evidence that points to the impairment of oxygen metabolism during progression of CRPS, probably as a result of hypoxia and microangiopathic changes (10). Birklein F. et al, documented increase in skin lactate in CRPS patients probably as a result of chronic tissue hypoxia (11). Regional blood flow abnormalities are found regularly in CRPS (5). CGRP and Substance P release could explain vasodilatation and edema and indeed one study found CGRP to be increased in CRPS (18). CGRP (6) also has been documented to be increased in migraine. Deshayes P (22) indicated in order to define the course of vasomotor changes both Thermography and Capillaroscopy could be considered. Thermography demonstrates thermic gradiens in Phase I, hyper or isothermia in Phase II, and hypothermia in Phase III. Capillaroscopy can demonstrate pericapillary edema, venulo-capillary stasis and tortuosities which are only significant by their associations (22). Thermography can image neuropeptide sensitive microcirculation/arteriovenous anastomoses.

Although as a rule capillaries are regarded as being the only communication between arteries and veins, the presence of AVAs in certain organs has long been known. They were first described by Lealis-Lealis in 1707 in the male genital organs. An article by Clark in 1938 and a monograph by Clara in 1939 give excellent reviews of the literature (23).

Blood vessels are distributed profusely immediately beneath the skin. Especially important is a continuous venous plexus that is supplied by inflow of blood from skin capillaries. In most exposed areas of the body-the hands, feet and ears, blood is also supplied to the plexus directly from small arteries to highly muscular ateriovenous anastomoses. The rate of blood flow into the skin venous plexus can vary tremendously - from barely above zero to as great as 30% of the total cardiac output (24).

Popoff in 1934 published the digital vascular system (25). The digital arteriovenous anastomoses of the Sucquet-Hoyer type contains a zone of ateriovenous anastomoses located a little deeper than the web of the subcapillary arteries and veins. He indicated that the arteriovenous anastomoses must be considered as a peculiar peripheral neurovascular anatomic unit of complicated structure and important function.

The Sucquet-Hoyer canal-the entire anastomotic unit includes:
1) Afferent artery;
2) Sucquet-Hoyer canal;
3) Neuroreticular and vascular structures around the Sucquet-Hoyer canal;
4) The outer lamellated collagenous tissue and
5) the primary connecting veins.

He indicated that the entire muscular coat of the Sucquet-Hoyer canal is surrounded by a wide clear zone consisting of delicate collagenous reticulum and containing numerous nonmedullated nerves. Anatomically, arterio- venous anastomoses are div ided into two groups. The first group belongs to the

arteriovenous anastomoses of the Sucquet-Hoyer type. In man, these anastomoses are under control of the vasomotor nerves and their function is to divert rapidly the flow of blood from arteries directly into veins. For this reason, Sucquet chose for these anastomoses the name canaux derivatifs. They regulate both local and general temperature. The arterio-venous anastomoses of the second group are the direct anastomoses between arteries and veins of larger caliber. Thermography observation on rats with experimental neuropathic pain indicate the role of neural impulse activity on microcirculation and arteriovenous anastomoses (26).

Goldfert (27) in 1998 indicated that peripheral blood flow can be regulated by specialized vessel segments the arteriovenous anastomoses. Their wall consists of relatively thick layer of smooth muscle cells and the so-called epithelioid cells. The epithelioid cell is a specialized myogenic cell phenotype expressing nitric oxide synthase. He studied the innervation pattern of the different segments of the arteriovenous anastomoses in the rabbit ear using antisera against neuropeptide Y, tyrosine hydroxylase, CGRP, and substance P, as well as neuron specific enolase, calbindin D and neurotubulin and reported a correlation of the innervation pattern with epithelioid cell type in arteriovenous anastomoses and suggested that the epithelioid cells of the AVAs are controlled by a dense network of neuropeptidergic nerve fibers in functional connection to their paracrine role as a nitric oxide producer.

Molyneux GS (14), et al, studied the structure innervation and location of arteriovenous anastomoses in the equine foot and found that the innervation of the AVAs are more dense than that of the arteries and consisted of adrenergic and peptidergic nerves. Noradrenaline and neuropeptide Y containing nerves were identified as the vasoconstrictor components of the nerve supply and occurred along arteries and formed dense plexuses around AVAs. CGRP, substance P and VIP are vasodilators and were present in single nerve fibers which accompanied arteries and AVAs along the length of the dermal laminae. He suggested that the release of vasoactive peptides from diseased organs at a remote site may induce inappropriate prolonged vasodilatation of the AVAs.

Figueroa JM (28), et al, compared vascular innervation patterns in patients with and without symptoms of chronic rhinitis by immunohistochemical study of the nasal mucosa for the following neuronal markers: protein gene product 9.5 (PGP), CGRP, substance P, C termial peptide of neuropeptide Y (CPON).The following classes of vessels were identified: arteries, sinusoids, veins and arteriovenous anastomoses. Each vessel type had a characteristic innervation pattern, differing in the amount of fibers and their distribution within the adventitial and muscle layers. Rhinitic arteries and AVAs displayed a rich innervation than did nonrhinitic blood vessels.

Isidor Muffson (29) studied the responses of abnormal arterial circulation to various stimuli, i.e., intra-arterial histamine, papaverine, aminophylline, adrenaline, sympathectomy, Etamon and pain by use of radioactive sodium and suggested the possibility that the effect of histamine is mainly on the minute vessels and capillaries while that of sympathetic block is on the arteriovenous anastomoses.

Also literature gives references to AVAs in other organs like stomach, lung, heart and in the pathophysiology of Raynaud's phenomenon (30).

The pathophysiology of dynamic changes in regional perfusion / microcirculation associated with central pain mechanisms, e.g., RSD, CRPS, and migraine, can be better understood by utilizing Thermography to:
1) image neuropeptide sensitive microcirculation /AVAs,
2) evaluate preexisting vasomotor tone (31), and
3) to study their response to vasomotor and pharmacological challages. This will help us to clinically correlate the vasomotor processes that are encountered in migraine and CRPS/RSD.

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