

## **Cerebral arterio/venous transit time in multiple sclerosis: contrast ultrasound evaluation**

*Marcello Mancini<sup>1</sup>, Vincenzo Brescia Morra<sup>2</sup>, Orlando Di Donato<sup>3</sup>,  
Valentina Maglio<sup>3</sup>, Elena Salvatore<sup>3</sup>, Raffaele Liuzzi<sup>1</sup>, Roberta Lanzillo<sup>2</sup>,  
Arturo Brunetti<sup>3</sup>, Vittorio Iaccarino<sup>3</sup>, Marco Salvatore<sup>3</sup>*

*<sup>1</sup>IBB-CNR, Naples, Italy. <sup>2</sup>Department of Neurological Sciences. Federico II University School of Medicine, Naples, Italy. <sup>3</sup>Department of Biomorphological and Functional Science. Federico II University School of Medicine, Naples, Italy*

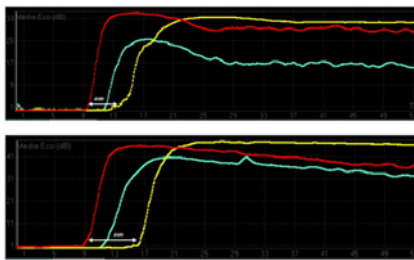
Despite the proposal of inflammatory, infective, and autoimmune factors as pathogenic agents Multiple Sclerosis (MS), their causative relation with its aetiology still remains to be elucidated.

Frequent edematous onionskin changes on the vein wall and vascular occlusions have been documented in the early pathologic studies. These findings indicate that hemodynamic abnormality could be a significant component in the pathophysiology of MS lesions. Contrast enhanced ultrasound (CUS) is an imaging tool for assessment of microcirculation in vivo.

78 patients affected by clinically defined MS (31 RRMS, 18 PPMS, and 29 SPMS ), and 36 age- and sex-matched control subjects underwent to CUS examination of the neck with 9-3 MHz wide-band transducer (Philips iU22). An area showing carotid artery and IJV in the same transverse plane at level of thyroid gland, was designated for analysis. For each side a bolus of 2.4 ml of SonoVue (Bracco SpA, Milan, Italy) was injected in left antecubital vein, followed immediately by 10 ml saline solution bolus. The wash-in curve was analysed off-line in a blinded way, using the time-intensity curve analysis program (QLab-Philips) in two manually defined regions of interest at level of carotid artery and internal jugular vein. Time To Peak (TTP), Arrival Time (AT), and Absolute Intensity Peak (AIP) were measured; the difference between AT in artery and AT in jugular vein was considered as Artery/Venous Transit time (A/Vtt). The MS patients EDSS score ranged from 1.5 to 6.5 (median 4.5). The contrast agent was well tolerated in all individuals without any side effects. Jugular reflux of contrast

agent was observed with a higher frequency in MS patients (30/78 (38%) MS patients and 7/35 controls (19%);  $\chi^2=3.84$  p=0.049). No significant differences were found between the MS and control groups in Arrival times, Time to Peak, and Absolute Intensities. A/Vtt was significantly prolonged in MS subjects compared with the control group (mean A/Vtt MS patients 5.9 (2.6-17.5), controls 4.8s (2.6-7.0); p=0.001). No correlation was found between A/Vtt and EDSS score and between A/Vtt and duration of the disease.

**Conclusions:** The A/Vtt, evaluated at the level of jugular veins, that in supine position are the main drainage pathway of cerebral blood, is prolonged in MS patients. Most of the transit time is for the contrast bolus to pass through arterioles, capillaries and venules. The observed changes are expected results since some degree of vascular pathology has often been described in pathological studies in MS. The prolonged artery/venous transit time that we observed in MS patients could be secondary to impaired microvascular function or a obstruction/reflux, affecting the hydrostatic pressure gradient, and reproduce the findings associated with Multiple Sclerosis CCSVI. Contrast Ultrasound could be a non invasive method to assess the microcirculatory impairment or venous outflow obstructions in MS patients.



Time-intensity curve analysis. The red lined curve depicts the arterial signal, the green lined curve represents tissue signal and yellow lined curve represents the venous signal. The A/Vtt was 3.3s in a control subject (top) and 6.9s in a MS patient (bottom).