The term Mild Cognitive Impairment (MCI) was introduced for the first time in the scientific literature to identify individuals who were not cognitively normal for age and yet did not have overt dementia [1]. It can be described as a transitional period between normal ageing and the diagnosis of clinically probable very early dementia. The existence of a cognitive continuum from normal aging to dementia through a phase of mild compromising has been suggested [2]. Several studies have shown that in a subset of subjects, in particular those who are destined to develop dementia, there is a decline in cognitive function that can be very subtle at first. The construct of MCI proposes to identify these individuals at an earlier point in the cognitive decline such that if therapeutic interventions become available, clinicians can intervene at this juncture. In particular, the concept of MCI refers to a population of elderly subjects who are not compromised in their daily functioning, but show a subclinical and isolated cognitive deficit and are potentially at risk of developing dementia [3]. Not all subjects with mild cognitive impairment necessarily develop the disease. Over the years several terms have been used to describe subclinical cognitive deficits associated with aging such as “benign senile forgetfulness” [4], the “Age-Associated Memory Deficit” (AAMI) [5] or “cognitive decline associated with age” [6] (AADI), and whilst it was originally felt to reflect a stage of normal ageing, more recent data have cast some doubt on that. So, MCI has come to be recognized as a pathological condition, i.e. not a manifestation of normal ageing, and has received a great deal of attention as a clinically useful entity. Numerous epidemiological studies have documented the accelerated rate of progression to dementia and Alzheimer’s disease (AD) in MCI subjects and certain predictor variables appear valid [7]. There is no agreement in the field on a single set of criteria for diagnosing MCI, but it represents a useful clinical entity with an almost unknown pathogenesis. It is most important to realize that MCI is a clinical diagnosis which is the same as are the diagnoses of dementia or AD. Whilst cognitive tests and functional measures are very useful, ultimately, the final determination relies on the clinician’s judgment. AD is certainly the most common form of dementia. It can be defined as a progressive neurodegenerative disorder. Its pathological hallmarks include: plaques composed by amyloid-β aggregates, neurofibrillary tangles composed of hyperphosphorylated tau, granulovacuolar degeneration, neuronal and synaptic loss [8-10]. The exact mechanism that causes these changes in the brains is not completely understood; however it is clear that the disease arises from no single cause but from the cumulative result of many risk factors. The most accepted hypothesis is that amyloid-β deposition causes the cascade leading to neuronal degeneration. In addition, recent studies have shown that vascular factors play a role in this process. There is increasing evidence regarding vascular changes in AD: capillary cerebral atrophy, focal constriction, amyloid-β deposition in the vessel’s walls is some of these microvascular changes [11]. Recent data show that vascular endothelial dysfunction observed in AD patients compared with their controls would most likely represent the lowest common denominator underlying these pathogenic mechanisms [12]. Over the past decade, a non-invasive technique has evolved to evaluate endothelial function: the Flow-Mediated Vasodilation (FMD). FMD is a commonly used, reproducible, and accurate method of measuring the brachial artery diameter after reactive hyperemia. This stimulus provokes the endothelium to release Nitric Oxide (NO) with subsequent vasodilation that can be imaged and quantitated as an index of vasomotor function [13]. In the past 10 years, there has been a virtual explosion in the literature concerning the construct of mild cognitive impairment. The interest in this topic demonstrates the increasing emphasis on the identification of the earliest features of cognitive disorders such as AD and other dementias. Mild cognitive impairment represents the earliest clinical features of these conditions and, hence, has become a focus of epidemiological, neuroimaging, biomarker, neuropathological and disease mechanism research as well as clinical trials. Increasing evidence emerged from the literature of the last few years regarding the pathogenesis of dementia; in particular about the dominant role of vascular factors in the pathogenesis of AD. Atrophy of brain capillaries, focal vasoconstriction, structural changes of endothelial cells and the deposition of amyloid-β in the vascular walls appear to be
major vascular changes. The best hypothesis is that underlying these changes there is the toxic effect of amyloid-β on endothelial cells with a subsequent endothelium-dependent vasoconstriction. Several studies noted the presence of endothelial abnormalities in patients with AD using serum markers of endothelial dysfunction (E-selectin, thrombomodulin, adhesion molecules) or measuring the vascular response to iontophoresis of acetylcholine. Among these, an important clinical study by Didem et al. [12] observed a significant correlation between the values of FMD and AD. In this study the endothelial function was assessed by means of the FMD technique. Determining endothelial function from peripheral arteries can reflect vascular endothelium in the brain. This was proved in an experimental study showing that cerebral vessels respond like peripheral vessels to acetylcholine infusion. On the basis of these evidences a recent study showed for the first time the existence of a close relationship between endothelial dysfunction and mild cognitive decline [14]. Reported data support the hypothesis of a pivotal role of vascular factors in the pathogenesis of cognitive decline. In particular, what emerges is the existence of an alteration of the endothelium already at this very early stage of cognitive deterioration. The hypothesis is that this condition is attributable to the role of the protein amyloid-β that may be responsible for neuronal cell damage through the mechanism of lipid peroxidation and production of reactive oxygen species; impaired vascular endothelium may have a role in accelerating this phenomenon. In the pathogenesis of MCI seem to play a role the vascular factors, which may represent new therapeutic targets in the next future. In this regard the technique of FMD has proven effective in evaluating these patients, allowing an easy, non-invasive and accurate study of the endothelium; therefore it could be considered a valid tool for clinical diagnostic and prognostic classification of MCI in addition to imaging and laboratory tests.

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REFERENCES