

《会長要請講演 I》

Detection of Early Alzheimer's Disease

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Functional brain imaging has been used extensively to characterize pathophysiological changes associated with Alzheimer's disease and other types of dementia. One of recent research efforts is to develop clinical and laboratory methods that can detect the disease in very early stage. This will allow patients to be treated prior to substantial loss of neurons. A clinical category, mild cognitive impairment (MCI), is to identify patients who have increased likelihood of developing dementia in subsequent years. This group of patients permits investigations of early pathophysiological signatures of Alzheimer's disease, which, in return, helps the detection of Alzheimer patients among MCI patients. However, the clinical significance of early treatments with currently available drugs has been debated. There is inconsistency as to outcome of early drug treatments in MCI patients. Functional brain imaging may unveil heterogeneity of MCI patients and potentially provide prognostic and therapeutic indices, but due to lack of substantial evidence to support such notions, the reimbursement for clinical FDG PET applied in MCI group is not currently approved in the US. These factors prompted the initiation of multi-center trials to characterize better brain imaging findings of MCI patients in a longitudinal manner. In parallel, there is a growing enthusiasm to use functional brain imaging as a part of new drug developments for dementing disorders. The use of functional brain imaging potentially permits rapid and quantitative evaluation of drug treatments in human patients, both mechanistically and clinically.

《会長要請講演 II》

Detection of Early Coronary Arteriosclerosis

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Measurements of myocardial blood flow and of its response to pharmacological and physiological stress, now available with PET, offer the non-invasive evaluation of coronary circulatory function. Hyperemic myocardial blood flow as stimulated with adenosine, dipyridamole or ATP reflects the integrated vasodilator capacity including both vascular smooth muscle and endothelium-dependent vasomotor control. Responses of blood flow to sympathetic stimulation with cold pressor testing offer information endothelium-dependent determinants of coronary circulatory control. Further, the distribution of hyperemic blood flow from the base to the apex of the left ventricle can provide information on the functional and structural integrity of the epicardial coronary conduit vessels.

Current diagnostic approaches identify alterations and myocardial perfusion, function or metabolism due to significant coronary stenosis. Therefore, these approaches detect coronary artery disease at a fully developed and thus late stage. Importantly, functional alterations especially of the coronary endothelium participate in the early disease process. Delineation of these functional alterations through measurements of blood flow with PET provides then a means for early disease detection. Under normal conditions, the endothelium protects the integrity of the arterial wall. If dysfunctional, the endothelium promotes atherosclerosis. Endothelial dysfunction is associated with an abnormal vasoreactivity that modifies flow responses to pharmacological and physiological challenges. Characteristically, risk factors for coronary artery disease like hypercholesteraemia, diabetes, smoking and low estrogen levels after menopause have been found to result in reductions in the total vasodilator capacity. Diminished, absent or even paradoxical flow responses to sympathetic stimulation observed in diabetes, hypercholesteraemia, smokers and post-menopausal women point to endothelial dysfunction as the reason for the diminished total vasodilator capacity. Importantly, as several investigations have demonstrated, these functional alterations appear to be reversible. For example, risk factor modification through cardiovascular conditioning and a low-fat diet, through cholesterol lowering with HMG-CoA reductase inhibitors, anti-oxidant treatment with vitamin C, or diabetes control can improve the total vasodilator capacity and, flow responses to cold-pressor testing. These improvements in coronary circulatory function are most likely mediated through a beneficial effect of risk factor modification on endothelial function.

Several studies have indicated that endothelial dysfunction is an independent predictor of cardiovascular morbidity and mortality. Consequently, identification of endothelial dysfunction through non-invasive measurements of myocardial blood flow in individuals with risk factors for coronary disease could identify those patients at the highest risk for future cardiovascular morbidity and mortality. Conversely, demonstration of beneficial effects of risk factor modification on endothelial function could then serve as a measure of reduction in coronary risk.