Potential of ^{18}F -FDG PET to evaluate the cardiocerebral interaction

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Heart failure (HF) with a reduced ejection fraction is a clinical syndrome caused by any condition that damages or weakens the heart. The etiology of HF is complex; therefore, the heart's interaction with the brain, among other vital organs, shares various pathophysiological mechanisms.¹ For example, Takotsubo cardiomyopathy (TC), also known as acute stress-induced cardiomyopathy, is a typical disease recognized as an established clinical entity of several heart–brain disorders. Up to 85% of patients with TC experience either significant emotional or physical stress.²

The metabolic interaction between the heart and brain is understandable in clinical practice and often affects patients' outcomes such as stroke, mental disturbances, and cognitive impairment. Cardiac complications are common in patients with cerebrovascular disease. In fact, a 2- to threefold increased risk of stroke among patients with HF has been reported.³ Depression in patients with chronic physical disease including HF has become a major focus of research in recent years.^{1,4} Patients with HF with depression as a comorbidity have a significantly higher mortality rate.⁵ Cognitive impairment, which confers an increased risk of clinical dementia that may coexist with depression, is also associated with HF.⁶

Havakuk et al.⁷ defined “cardiocerebral syndrome” as follows: a state of cognitive impairment of undefined cause in patients with HF, beyond that anticipated in age-matched controls, and typically accompanied by anatomical brain changes. However, the mechanisms underlying metabolic alterations in the brain in patients with HF are still not well known.

A study using 3 T magnetic resonance imaging (MRI) demonstrated that the occurrence of cerebral cortical microinfarcts in patients with HF is higher than that in reference participants, which is related to an adverse vascular risk factor profile and severity of cardiac dysfunction.⁸ Almeida et al. showed that patients with HF exhibit a relative loss of cerebral gray matter in various cortical and subcortical regions extending to the frontal, anterior cingulate, and temporal–parietal lobes based on MRI that revealed a close relationship with cognitive and emotional processing.⁹ Several studies have shown that cerebral blood flow (CBF) in patients with HF is significantly decreased compared to that in healthy subjects.¹⁰ Various brain sites including the temporal, parietal, and occipital regions, which could be related to controlling autonomic, cognitive, and mood functions, have been observed with relatively reduced CBF. Although biochemical markers have received considerable attention for Alzheimer's disease in recent years, Kresge et al. found an interaction between the left ventricular ejection fraction (LVEF) and cerebrospinal fluid biomarkers in participants with normal cognition, whereas lower LVEF is associated with increased total tau and phosphorylated tau.¹¹

In this issue of the *Journal of Nuclear Cardiology*, Yun and colleagues report their investigation of the metabolic heart–brain interaction in patients with HF with a reduced ejection fraction using ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT). The importance of

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Figure 1. Possibility to assess cardiac and brain function using FDG PET/CT. ^{18}F -fluorodeoxyglucose (FDG) is an analog of glucose, and its uptake is a marker of cardiac and brain glucose metabolism. FDG positron emission tomography (PET)/computed tomography (CT) offers the possibility to understand the pathophysiological mechanisms of cardiocerebral syndrome.

this study is in determining if there is a relationship between cardiac function and the cerebral metabolic activity derived from FDG PET/CT in comparison with that in healthy volunteers. One of the unique points of this study is that they used serial FDG PET/CT scans for both heart and brain evaluations (Figure 1). The uptake of FDG is a marker of tissue uptake of glucose, which is closely correlated with certain types of tissue metabolism. FDG PET/CT is now widely used as a powerful imaging tool for the evaluation of various malignant tumors. However, the initial studies of FDG PET demonstrated clinical utility in evaluations of the heart and brain, and its potential role in the evaluation of refractory seizure disorders, dementia in brain imaging,¹² and myocardial viability in cardiac imaging¹³ have been demonstrated. Glucose is the fundamental metabolic substrate in brain tissue. Therefore, the uptake of FDG on PET reflects the metabolic activity in the brain, and FDG PET is used as a molecular imaging method to study global and local brain metabolism.^{14,15} Previous studies in patients with depression have indicated that metabolic abnormalities in specific cerebral regions, including the prefrontal cortex, temporal lobe, cingulate cortex, corpus striatum, and hippocampus, can be observed.¹⁶

In the study by Yun et al., patients with HF and healthy volunteers who underwent myocardial perfusion at rest by $^{99\text{m}}\text{Tc}$ -MIBI single-photon emission computed tomography/CT and cardiac and cerebral FDG PET/CT were prospectively enrolled. They categorized patients

with HF into four subgroups based on the extent of hibernating myocardium (HM) and LVEF as follows: Group 1, $\text{HM} < 10\%$; Group 2, $\text{HM} \geq 10\%$, $\text{LVEF} < 25\%$; Group 3, $\text{HM} \geq 10\%$, $25\% \leq \text{LVEF} \leq 40\%$; and Group 4, $\text{LVEF} > 40\%$. According to their results, the whole-brain metabolic activity is significantly reduced in patients with HF and shows a statistically significant positive relationship with HM and negative relationship with scarring. Moreover, they found an association between the region (bilateral frontal areas, bilateral hippocampus, and bilateral para-hippocampus) of brain metabolism and extent of HM. Among them, patients with HF with HM and moderately impaired LVEF preserved these cognition-related frontal areas. These results suggest that FDG PET/CT might be useful to contribute to the understanding of pathophysiological mechanisms underlying the cognitive impairment observed in patients with HF. However, unfortunately, as pointed out by the authors, cognitive impairment was not assessed in terms of brain function. Thus, the clinical meaning of reduced cerebral metabolic activity is unknown in the current study.

The Effects of Selective Serotonin Re-Uptake Inhibition on Morbidity, Mortality, and Mood in Depressed Heart Failure Patients (MOOD-HF) study showed that treatment with selective serotonin reuptake inhibitors does not result in significant improvements in depression, with no reductions in all-cause mortality or hospitalization in patients who are depressed and have HF.¹⁷ Therefore, a hypothesis that depression followed by HF does not have the same pathogenesis as that of primary depression is suggested.¹ Recently, Lyra et al. investigated brain glucose metabolism in patients with HF using FDG PET/CT.¹⁸ In their study, patients with HF showed whole-brain and regional brain hypometabolism compared to that in matched controls, similar to the findings of the study by Yun and colleagues. Furthermore, patients with HF and epiphenomenal or real depression showed different metabolic patterns with significant relative regional brain hypometabolism in the amygdala, hippocampus, and ventral prefrontal cortex implicated in the pathogenesis of depression. Accordingly, FDG PET/CT can diagnose depression related to HF.

While several imaging studies have attempted to elucidate the heart–brain correlation, FDG PET/CT may clarify the pathophysiological mechanisms in more detail, which may help guide therapy. We now need further long-term follow-up with data on the cognitive function of participants to understand whether FDG uptake in the brain is improved after HF therapy.

Disclosures

The authors have no conflicts of interest to disclose.

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