Heart failure (HF) is a highly prevalent disorder worldwide and, consequently, a burden on the healthcare systems of many nations. Although the effects of HF are systemic, many therapeutic targets are focused on cardiac dysfunction. The brain is closely related to the heart, but there are few reports on the relationship between these organs. We describe the effects of the brain on HF progression. Specific brain regions control sympathetic drive and neurohumoral factors, which play an important role in disease exacerbation. In addition, we review some of our previous studies on deranged cerebral metabolism and reduced cerebral blood flow during HF. Although the reasons underlying these effects during HF remain uncertain, we propose plausible mechanisms for these phenomena. In addition, the clinical implications of such conditions in terms of predicting prognosis are discussed. Finally, we investigate cognitive impairment in patients with HF. Cognitive impairment through cerebral infarction or hypoperfusion is associated with adverse outcomes, including death. This brief review of brain function during the development of HF should assist with future strategies to better manage patients with this condition. (Circ J 2015; 79: 942–947)

Key Words: Brain; Cerebral metabolism; Cerebrovascular circulation; Cognitive function; Heart failure

Central Nervous System (CNS) as a Source of Neurohumoral Drive in HF

Impaired cardiac function activates neurohumoral systems, particularly the sympathetic nervous system and the renin-angiotensin-aldosterone system, and contributes to the progression of HF. However, altered neurohumoral signals also activate the CNS, which plays a persistent role in regulating cardiac function. Some apparatuses of the brain function via crosstalk mechanisms with the heart and the production of neural reflex systems. The circumventricular organs of the lamina terminalis in forebrain regions primarily sense thirst or sodium intake and regulate volume status in HF. They lack a blood-brain barrier and therefore catch the signals of blood-borne neuropeptides. The paraventricular nucleus (PVN) of the hypothalamus is a center for fluid-balance regulation and sympathetic excitation. The PVN is located near the third ventricle in the forebrain and comprises different neuronal subgroups. The magnocellular neurons in the PVN project to the posterior pituitary and release humoral factors such as adrenocorticotropic hormone and arginine vasopressin, which may affect sodium and fluid retention. In addition, the PVN is mainly involved in regulating sympathetic drive. This process starts with the nucleus tractus solitarius, which transfers vagal and baroreceptor information to the PVN through afferent neural projections. The parvocellular neurons in the PVN integrate these data and influence sympathetic nerve activity. These neurons project to the rostral ventrolateral medulla and the intermedio-
HF and Brain Function

Reduction in CBF During HF

Brain vessels have autoregulatory functions to maintain blood flow over a diverse range of perfusion pressures. CBF is generally believed to be preserved during HF. Despite a marked decrease in cardiac output during HF, compensatory mechanisms exert every effort to redistribute blood flow towards vital organs and rescue cerebral perfusion. However, some evidence has suggested that certain HF patients have decreased CBF despite these compensatory mechanisms. Previously, we reported that global CBF estimated by radionuclide angiography was low in patients with advanced-stage systolic HF. We found in that study that global CBF was approximately 20% less in patients with HF than in control patients (40 ± 4 vs. 49 ± 4 ml·min⁻¹·100 g⁻¹, P<0.01).

Little is known of the mechanisms underlying impaired cerebral autoregulation in advanced HF. It is generally assumed that multiple factors are associated with cerebrovascular changes, which lead to increased vascular resistance. Neurohumoral or metabolic factors such as the renin-angiotensin system, endothelin, adiponectin, or other metabolites have been reported to be related to chronic vascular changes in HF. In addition, previous study has reported that endogenous vasoactive molecules, such as intracellular adenosine monophosphate, led to cerebral vessel changes in HF patients. However, we propose that these cerebral resistance vessels change as a result of a chronic adaptation to low cardiac output in advanced HF. A previous study showed that sustained alteration in cardiac output or systemic blood pressure can lead to structural changes in brain resistance vessels. In addition, it has been demonstrated that CBF is not affected by acute modulation of cardiac output. Similarly, we reported previously that CBF is associated with the serum B-type natriuretic peptide level and New York Heart Association functional class, which indicate the...
The possibility that disease chronicity may be associated with cerebral autoregulation to maintain CBF during HF suggests that CBF may inversely reflect disease duration and predict prognosis in HF patients. In recent years, we have focused on the prognostic value of CBF in patients with HF. We first investigated whether global CBF may be associated with death or the need for urgent heart transplantation in patients with advanced HF. We measured the CBF using radionuclide angiography, which was performed immediately after intravenous injection of a small amount of radioisotope (technetium-99m ethyl cysteinate dimer) that could be used to scan bilateral hemispheric CBF through a dual-head gamma camera. Despite only indirectly measuring the CBF, radionuclide angiography has some advantages as a detection method such as the requirement for only a small dose of radioisotope, which minimizes hemodynamic compromise, and a shorter scanning time than either MRI or ultrasonography.

In our current study, we enrolled 224 systolic HF patients with a left ventricular ejection fraction (LVEF) of less than 35% and analyzed the CBF in each case. We found that patients with low CBF were nearly 2.5-fold more likely to die or require urgent transplantation during a median follow-up period of 3 years (Figure 1). Moreover, the measurement of CBF showed a trend towards an improved prognostic predictive ability in addition to the V˙E/V ˙CO 2 slope, which is a parameter measured by a cardiopulmonary exercise test. However, this trend was not statistically significant. The main clinical implication of these findings is that CBF can be helpful in identifying advanced systolic HF patients who require urgent transplantation, even though they cannot undergo exercise testing to predict a prognosis.

Next, we investigated the possible role of CBF estimation in patients with idiopathic dilated cardiomyopathy (DCMP). Idiopathic DCMP is generally defined as a type of DCMP in which reversible causes of HF such as endocrine disease, pregnancy, tachycardia, and excessive alcohol consumption are ruled out. The prognosis and its determinants in cases of idiopathic DCMP have been infrequently reported. Our analyses revealed that CBF is associated with improvement in LVEF measured at the 1- and 2-year follow-up visits compared with baseline data taken at the time of initial diagnosis. Interestingly, we found that HF symptom duration was also an independent factor predicting the recovery of left ventricular systolic dysfunction and it mildly correlated with CBF in those patients (r=−0.334, P<0.001). Until now, the precise mechanism by which CBF can reflect disease chronicity, and how cerebral vessels can be adapted in accordance with HF progression, remains unknown. However, our current study findings imply that the measurement of CBF, which may reflect the level of crosstalk between the heart and brain, can assist with predicting adverse outcomes in advanced HF patients.

**Deranged Cerebral Metabolism in HF**

Abnormal cerebral metabolism has been reported during HF as a result of dysregulated CBF. However, few data exist on the changes that occur in cerebral metabolites during HF. Brain tissue consumes a large amount of energy obtained from the oxygen-dependent metabolism of glucose. However, there are currently no data suggesting abnormal brain glucose metabolism during HF. The brain uses metabolites, such as ketones, medium chain fatty acids, and amino acids, as alternative energy sources. Despite the scarcity of data on cerebral metabolic abnormality, we have reported some metabolic abnormalities in HF patients.

To detect metabolic changes in the brain, we used proton magnetic resonance spectroscopy (1H MRS). This technique was performed following T1-weighted MRI from 2 localized brain regions of parietal white matter (PWM) and occipital gray matter (OGM). The absolute concentrations of the cerebral metabolites (N-acetylaspartate, creatine, choline, and myoinositol) were thereby calculated.

![Figure 2. Changes in cerebral metabolite levels after heart transplantation.](image_url)
We first compared the cerebral metabolite profiles in HF patients and healthy control subjects. In the PWM, only the creatine level was significantly lower in the HF compared with control subjects (6.61±0.93 vs. 7.47±0.69 mmol/kg, P<0.01), whereas all 4 metabolite levels were decreased in the OGM of HF patients (creatinine, 7.60±1.32 vs. 8.86±0.52 mmol/kg, P<0.01; N-acetylaspartate, 9.72±1.52 vs. 10.57±1.23 mmol/kg, P<0.05; choline, 1.44±0.23 vs. 1.62±0.16 mmol/kg, P<0.01; myo-inositol, 5.54±1.38 vs. 6.87±1.14, P<0.01). Creatine levels were found to be independently associated with the half-recovery time (the time required for a 50% fall in the peak oxygen consumption rate as measured by cardiopulmonary exercise test), the duration of HF symptoms in the PWM (r=-0.56, P<0.05), and with the peak oxygen consumption rate and serum sodium level in the OGM (r=0.58, P<0.05). These findings suggest that cerebral metabolic dysregulation may be used to evaluate disease severity and prognosis in HF.

When we assessed cerebral metabolic abnormalities in patients with advanced HF, the occipital N-acetylaspartate level was found to be an independent predictor of death (hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.41–0.67; P=0.001). This suggests that cerebral metabolism may provide new prognostic insights for such patients. In addition, we measured the level of cerebral metabolites serially before and at 2 and 12 months after cardiac transplantation. Cerebral metabolic abnormalities were found to have improved after successful cardiac transplantation. However, there were regional differences in the recovery of metabolic abnormalities (Figure 2). In the OGM, the levels of creatine, choline, and myo-inositol had gradually recovered at the 12-month follow-up compared with baseline. In the PWM, the level of myo-inositol showed a similar pattern of recovery, but the choline level was highest at 2 months, and then approached normal levels at 12 months. In contrast, the parietal N-acetylaspartate level tended to decline at the 12-month follow-up compared with baseline, and the creatine level initially improved but later decreased.

Creatine is critical for cerebral energy metabolism and reserve. It is converted to creatine phosphate by creatine kinase in the brain, which buffers the ATP concentration in response to high-energy demands. Thus, abnormal levels of creatine can lead to brain dysfunction such as cognitive impairment. Creatine is formed in the human body and maintained at relatively stable levels. Creatine levels are also believed to be stable in the brain. However, we have previously demonstrated that the creatine levels decreased in the PWM and OGM during HF. In terms of the essential role of creatine as a brain fuel, HF patients are thought to have a cerebral energy deficit. In order to rule out the confounding effect of serum osmolarity on the levels of cerebral metabolites, we measured myo-inositol, a marker of reversible cerebral osmolytes. However, osmolar changes were mild in both brain regions in our HF cases. These data support the notion that there is a cerebral energy deficit with regional differences during HF.

N-acetylaspartate is used as a neuronal marker, and the loss of its expression is believed to indicate neuronal loss. In our previous study, N-acetylaspartate in the OGM was found to be the only strong predictor of mortality in HF patients. This implies that neuronal damage may occur in the gray matter during the course of HF progression, reflecting a poor prognosis. Interestingly, changes in the metabolite levels in the white matter were not found to reflect the HF prognosis. Although the cause of the difference between the 2 brain regions in terms of HF prognosis prediction remains unknown, regional susceptibility to cerebral hypoperfusion and combined hypoxic injury is believed to be a plausible explanation. Moreover, there is controversy as to whether loss of N-acetylaspartate can be reversible according to disease activity. After cardiac transplantation, the levels of N-acetylaspartate were not significantly changed in the PWM and OGM. Susceptibility to cyclosporine toxicity may contribute to slight changes in the N-acetylaspartate levels. However, further investigation is needed to clarify the reversibility of neurons after HF recovery and the prognostic implications of this.

**Impaired Cognitive Function During HF**

Cognitive function is composed of various domains, including memory, attention, executive functioning, psychomotor speed, language, and visuo-spatial ability. Cognitive impairment is a broad term that generally describes a decline in cognitive function. Many reports have indicated that cognitive impairment is highly prevalent in HF, affecting between 30% and 80% of patients. HF patients are known to suffer from impairment in various aspects of cognitive function involving working memory, attention, problem solving ability, and psychomotor response, but the language domain, including visuo-spatial ability, has not been sufficiently investigated.

The mechanisms underlying the development of cognitive impairment in HF are yet to be elucidated, although multiple hypotheses have been suggested. For example, cerebral infarction caused by cardiac mural emboli has been proposed. Left ventricular systolic dysfunction combined with blood stasis in the dilated chamber is likely to form a thrombus leading to cerebral infarction. Mural thrombi are commonly observed in cardiomypathy patients with severe left ventricular systolic dysfunction. Patients with HF are believed to be in a hypercoagulable state because of impaired endothelial dysfunction or rheological abnormalities, which may activate platelet adhesion to the endothelium and a coagulation cascade subsequently leading to thrombosis. Another theory is based on regional cerebral ischemia from chronic hypoperfusion. Many animal and human studies have shown that the medial temporal lobe, including the hippocampus, which plays a key role in cognitive processing, is particularly vulnerable to chronic CBF reduction. A functional imaging study has reported cerebral hypoperfusion in the pre-cuneus and posterior cingulated gyrus, which are connected with the medial temporal structures and appear to correlate with episodic memory in HF patients. Other studies have demonstrated that HF patients have reduced regional CBF in the posterior cortices associated with visual memory, which is similar to the region of brain hypoperfusion in early stage Alzheimer’s disease. This cerebral hypoperfusion hypothesis is supported by evidence for an improvement in cognitive impairment after implantation of left ventricular assist devices. There have been additional explanations proposed for the development of cognitive impairment in HF, such as sleep apnea, dysrhythmias, hypervolemia, and elevated neurohumoral substances. Nevertheless, the exact mechanism and the causal relationships underlying cognitive impairment in HF patients remain unclear.

Several studies have demonstrated that cognitive impairment is associated with a decrease in the quality of life of HF patients. Cognitive function is central to the performance of basic activities of daily living. In addition, it is important that HF patients understand and participate in HF treatment plans. However, a large proportion of HF patients suffer from loss of memory and difficulties in concentration. These functional impairments can adversely affect the recognition of HF symptoms, and adherence to complex medication and dietary
regimens. Moreover, cognition is known to be a component of frailty. Thus, the risk of falling increases in HF patients with cognitive impairment. It is unclear how cognitive impairment may augment the risk of frailty, but some data suggest that it is associated with declines in gait, balance, and stepping. In addition, cognitive impairment is reported to progress to dementia in HF patients. A previous longitudinal study incorporating a 9-year follow-up period reported that HF patients with lower cognitive performance were at increased risk of progression to dementia in HF patients. A previous meta-analysis revealed a deterioration in neuropsychological performance, including cognitive function, memory, and psychomotor speed/attention, when comparing HF patients with control subjects (odds ratio, 1.62; 95% CI, 1.25–2.61). Furthermore, a previous meta-analysis revealed a deterioration in neuropsychological performance, including cognitive function, memory, and psychomotor speed/attention, when comparing HF patients with control subjects (odds ratio, 1.62; 95% CI, 1.25–2.61).

These overall problems may be associated with a huge clinical effect on patient outcomes such as death or hospital readmission. A prospective cohort study of older adults hospitalized with a primary diagnosis of HF showed that patients with moderate-severe cognitive impairment were significantly more likely to die or be readmitted to hospital at 6 months compared with patients with no impairment (adjusted HR, 1.60; 95% CI, 1.03–2.48; P=0.04). The substudy of the Trial of Intensified vs. standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) also reported that severe cognitive impairment was related to higher mortality (HR 1.53, 95% CI 1.02–2.30, P=0.04).

Conclusions

Many recent clinical trials have failed to reverse left ventricular systolic dysfunction and adverse outcomes in HF. Until now, the treatment plan for HF has mainly focused on the recovery of cardiac function. However, HF is a systemic disease in which its specific pathophysiology, which involves low cardiac output and activation of neurohormones, affects the whole body. Thus, treatment strategies limited to the heart may be unsuccessful. The brain is closely related to the heart and thus, may play a role in the progression of HF. Sympathetic activation and regulation of fluid homeostasis through the brain is one of the most important causes of left ventricular remodeling and symptom aggravation in HF. In contrast, low cardiac output can impair autoregulation of cerebral vessels and reduce CBF in HF. Cerebral hypoperfusion is associated with cerebral metabolic abnormalities and cognitive impairment, which reflect poor outcomes in HF. Considering the bidirectional heart-brain interconnection, it seems beneficial these days to evaluate brain function to determine the prognosis and as part of a therapeutic strategy for HF when HF management is at the breaking point. However, mechanistic data on this crosstalk should be further investigated.

References
