Review

Molecular Imaging Using Positron Emission Imaging in Heart Failure

Yen-Wen Wu

Abstract
The incidence of heart failure (HF) is increasing and it remains the only area in cardiovascular disease wherein hospitalization rates and mortality have worsened in the past 25 years. This review discusses the roles of molecular imaging using positron emission tomography in HF, including perfusion, metabolism, viability, innervation, and inflammation, and provides new insights into the pathophysiology and therapeutic strategy of HF.

Key Words  heart failure  ·  molecular imaging  ·  positron emission tomography  ·  perfusion

Background
The incidence of heart failure (HF) is increasing and it remains the only area in cardiovascular disease wherein hospitalization rates and mortality have worsened in the past 25 years. HF presents and evolves as syndromes which result from any structural or functional impairment of ventricular filling or ejection of blood, including reduced left ventricular (LV) ejection fraction (EF) (HFrEF), preserved LVEF (HFpEF), and mid-range ejection fraction (HFmrEF). Despite treatment advances, the mortality rate of HF has increased steadily. More patients survive myocardial infarction (MI) due to better standards of care, and consequently this increases the number of patients who subsequently develop HF. HF places a significant burden on patients, carers and healthcare systems. Determinants and outcomes of HF remain unclear. With each acute event, myocardial injury...
may contribute to progressive LV dysfunction. Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality. HF mortality remains high, with ~50% of patients with HF dying within 5 years of diagnosis, even after improvement of treatments (1-5).

Limited progress has been made in identifying evidence-based effective treatments for HF over the last few decades. Potential contributors include an incomplete understanding of pathophysiology and poor matching of therapeutic mechanisms. Besides contractile function, molecular imaging could be used to evaluate myocardial perfusion, metabolism, viability, innervation, inflammation, angiogenesis, and cell death, and gains insights into cardio-oncology, dys-synchrony, and risk stratification (6,7).

This mini-review will focus on the roles of molecular imaging from the standpoints of myocardial perfusion, metabolism, viability, innervation, and inflammation, using positron emission tomography, to provide new insights into the pathophysiology and therapeutic strategy of HF.

**Myocardial Perfusion**

Patients with HF are initially classified based on the etiology of their disease, i.e., ischemic or non-ischemic cardiomyopathy. The diagnosis of HF is clear if prior myocardial infarction (MI) is reliably documented. Dynamic positron emission tomography (PET) myocardial perfusion imaging (MPI) used in conjunction with tracer kinetic modeling enables the quantification of absolute myocardial blood flow (MBF). Cardiac PET with perfusion tracers, such as $^{15}$O-water, $^{13}$N-ammonia, $^{82}$rubidium, and $^{18}$F-flurpiridaz allows non-invasive and absolute assessment of regional and global MBF. In conjunction with stress, regional and global coronary flow reserve (CFR) can also be calculated, which is the ratio between MBF at peak stress and MBF at rest. CFR measures not only vasodilator capacity but also endothelial reactivity of the coronary circulation, allowing non-invasive quantitative assessment for patients with diffuse coronary luminal narrowing or microvascular dysfunction (8).

In patients with coronary artery disease (CAD), a reduced CFR was shown to have prognostic implications, being a more sensitive predictor for cardiac death than was reduced LVEF, and associated with major adverse cardiovascular events (MACE). In addition, the presence of coronary vascular dysfunction in patients with normal or non-obstructive CAD predicts adverse cardio-vascular outcome. In symptomatic patients without overt CAD, impaired CFR was independently associated with diastolic dysfunction and adverse events, especially HF with preserved EF hospitalization (9-11).

Coronary microvascular dysfunction is highly prevalent among at-risk individuals and is associated with adverse outcomes regardless of gender, even in the absence of overt coronary atherosclerosis. It may reflect the functional alteration of endothelium, such as hypertension, dyslipidemia, diabetes mellitus, smoking, obesity or metabolic syndrome; or structural alteration of microangiopathy, myocardial fibrosis or loss of capillaries. The systemic inflammatory state
may induce coronary endothelial inflammation, microvascular dysfunction, myocardial substrate shift, myocardial and interstitial fibrosis that contribute to high diastolic left ventricular stiffness and HF development, even with preserved LVEF.

Cardiac imaging with PET/computed tomography (PET/CT) allows measurement of coronary artery calcium (CAC), myocardial perfusion and coronary vascular function. A recent study showed that hyperemic MBF and CFR provide incremental information about the presence of CAD over CAC score and perfusion imaging parameters. The combined use of CAC, myocardial perfusion imaging and quantitative coronary vascular function may help predict more accurately the presence of obstructive CAD (12).

**Transplant Vasculopathy**
Cardiac allograft vasculopathy (CAV) is the leading cause of late mortality after heart transplantation. It is characterized by the diffuse concentric intimal of both epicardial and intramyocardial arteries, which is difficult to be assessed by traditional coronary angiogram. Intravascular ultrasound (IVUS) has been proposed to be the most sensitive method for diagnosis of early CAV. Effective non-invasive screening methods are needed. Due to the progressive and diffuse process involving the epicardial and microvascular coronary system, traditional stress MPI SPECT usually underestimates disease severity and extent of CAV. With the absolute-quantitative nature of dynamic PET, a good correlation was observed between plaque burden as determined by IVUS and CFR as assessed by PET. It provides improved detection and gradation of CAV severity over standard myocardial perfusion assessment and is predictive of major adverse events (13-15).

**Cardiac Sympathetic Activity**
Neurohormonal activation is a compensatory mechanism in HF and maintains perfusion to the heart; it is also responsible for the progression of HF, including cardiac remodeling, progressive impairment of ventricular function, symptoms and lethal arrhythmia.

The metaiodobenzylguanidine (MIBG) is an analog of norepinephrine, which could be used in imaging the myocardial sympathetic synapses, which could be helpful in risk stratification of patients with various cardiovascular diseases, including HF, atrial fibrillation, malignant ventricular arrhythmia, and sudden death, but might be useful in other cardiac autonomic dysfunction diseases such as diabetes mellitus and neurologic degenerative diseases. Both a decreased cardiac $^{123}$I-meta-iodobenzylguanidine (MIBG) activity and an increased washout rate are indicative of a poor prognosis in patients with chronic heart failure. It could be used to monitor the response to pharmacologic treatments or cardiac resynchronization therapy. The indications of imaging with $^{123}$I-MIBG can be used to identify a low risk group (H/M ratio>1.6) with Class II or III HF and which was approved by FDA in 2013. In 2016, Blue Cross Policy claimed that myocardial sympathetic innervation imaging with $^{123}$I-MIBG is considered investigational for patients with HF. Currently two large prospective clinical studies, Prediction of Arrhythmic Events with Positron Emission
Tomography (PAREPET II), and AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-ICD) are undergoing. $^{11}$C-HED has been used as PET tracer for $^{123}$I-MIBG, however, its short half-life of carbon-11 (20 min) significantly limited the clinical use. Several PET tracers, including $^{11}$C-meta-hydroxyepinephrine (HED), a norepinephrine analogue, and $^{11}$C-CGP12177, a beta-adrenoceptor antagonist, not only can be used to visualize global but also regional defects in myocardial sympathetic innervation. Longer half-life $^{18}$F-labeled presynaptic tracers such as $^{18}$F-N-[3-Bromo-4-(3-fluoro-propoxy)-benzyl]-guanidine (LMI1195) have been developed for clinical imaging. Although no PET radiotracers that target the autonomic nervous system have gained wide clinical use in the cardiovascular system (16-22).

Myocardial Viability

Myocardial viability, the evaluation of dysfunctional but viable myocardium, can be assessed by several imaging techniques. In conjunction with dobutamine, contractile reserve can be evaluated by either echocardiography or cardiac magnetic resonance imaging (MRI). Delayed contrast-enhanced MRI and contrast-enhanced CT can assess scar tissue. Myocardial perfusion SPECT evaluates either cell membrane or mitochondria integrity. $^{18}$F-fluorodeoxyglucose (FDG) can be used to assess glucose metabolism and to differentiate the hibernating myocardium from scar tissue. PET used with FDG remains the most reliable, non-invasive tool to assess myocardial viability, and tends to replace $^{201}$TI SPECT imaging in centers equipped with a PET/CT (23-30). For patients with HFrEF and ischemic cardiomyopathy, myocardial viability is crucial for treatment decision-making (31). The post hoc subgroup analysis of the PET and Recovery Following Revascularization (PARR-2) trial suggested that FDG PET-guided management reduces the composite of cardiovascular events in patients with ischemic cardiomyopathy in one medical center with an experienced imaging team (32).

Despite that several studies have emphasized the utility of viability imaging in identifying those patients who may benefit from revascularization, a recent meta-analysis shows confusing results (33). Patients with viable myocardium appeared to benefit from revascularization, but the same benefits were observed in patients without viable myocardium. Some suggested that this might be resulted from mixed traditional (SPECT and dobutamine echocardiography) and the advanced (MRI and PET) imaging techniques, but this was still not conclusive (34,35). A large prospective randomized trial regarding Alternative Imaging Modalities in Ischemic Heart Failure (AIMI-HF) was conducted in 2013 (36), and its outcomes are expected to complement the results of the Surgical Treatment for Ischemic Heart Failure (STICH) viability sub-study and the PET and PARR-2 trial to address the unsolved issue.

Myocardial inflammation

Inflammation is a key factor of a wide range of cardiovascular and myocardial diseases. Given the numerous implications of inflammatory processes in disease initiation and progression, functional
imaging modalities including PET represent valuable diagnostic, prognostic, and monitoring tools in patient management. Since increased glucose metabolism is a hallmark of inflammation, PET using FDG is the mainstay diagnostic test for nuclear imaging of (cardiac) inflammation. FDG PET may be useful in the study of inflammation process, but exposes some limitation in myocardium. Recently, new approaches using more specific tracers to overcome the limited specificity of FDG have emerged. Compared with the non-specific FDG, this is potentially a new biomarker that may be useful in evaluation of myocardial inflammation and predicting cardiac remodeling and progression towards HF. A recent animal study compared $^{68}$Ga-citrate, $^{68}$Ga-DOTATATE, and FDG in a post-infarct mouse model; it concludes that FDG with myocardial suppression is the most practical imaging marker for post-infarct inflammation. It could be also used in detecting myocarditis. (32-34). There are also some studies in human that emphasize the usefulness of the somatostatin receptor imaging in the assessment of sarcoidosis and infarction related myocardial inflammation. Cardiac sarcoidosis has been increasingly recognized. Prognosis is poor if these patients are untreated or undertreated. FDG-PET CT is a sensitive tool in diagnosis, correlates closely with the level of granulomatous inflammation and can be used to monitor response to therapy (36-38).

**Conclusions**
Advances in the molecular imaging may play an increasingly critical role in diagnosis, prognosis and clinical treatment of HF at different stages. It provides insights into the HF preventive strategies, tracking patients' clinical status, discovering novel drug therapies, and expanding indications for HF therapeutic devices, and gene or cell-based therapies, in the era of precision medicine.

**Acknowledgement**
This study was partly supported by the Ministry of Science and Technology of Taiwan (MOST 104-2314-B-418-008; 105-2628-B-418-002-MY2).

**Disclosure**
There is no conflict of interest.

**Reference**
2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and
treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC.  
_Eur J Heart Fail_ 2016;18:891-975.


32. Srichai MB, Jaber WA. Viability by MRI or PET would have changed the results of the STICH trial. *Prog Cardiovasc Dis* 2013;55:487-93.


