# A Brief Review in the Use of PET Imaging Post Cardiac Arrest

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## Introduction

Clinical management of cardiac arrest post-cardiopulmonary resuscitation remains ineffective at preventing high mortality in patients. Reperfusion injury after achieving the return of spontaneous contraction (ROSC) is thought to be the primary factor for this high mortality, yet the processes that lead to neurological damages and its prevention remain poorly understood.

Positron emission tomography (PET) provides a unique opportunity to study biomarkers related to reperfusion injury *in vivo* across time and space. This review will examine the history of several radioligands to evaluate changes in brain glucose metabolism, cerebral blood flow, oxygen metabolism, neuroinflammation, and cardiac function in patients and animals post cardiac arrest.

## Dynamics of brain glucose uptake and metabolism

The earliest studies used [18F]fluorodeoxyglucose ([18F]FDG) to compare brain glucose metabolism in patients of different outcomes weeks to months after sudden cardiac arrest. Between 1994 and 1999, three different groups showed cerebral metabolic rate of glucose metabolism (CMRglu) was significantly reduced in patients in a coma or vegetative state up to 12 months after sudden cardiac arrest 1–3. In 2008, Nakamura et al. compared patients who underwent hypothermia post cardiac arrest and compared CMRglu in patients with positive vs. poor outcomes. They found patients with poor outcomes tended to have lower CMRglu, first suggesting [18F]FDG PET could be used as a predictor for clinical outcomes4. This reduction in CMRglu is also seen in fetal lambs undergoing asphyxiation via umbilical artery occlusion. When measured 4hr after 14 min of asphyxia, lamb fetuses showed significantly reduced CMRglu compared to control5.

Recent preclinical studies investigated fast temporal dynamics of glucose uptake in the brain during and shortly after induced cardiac arrest. In 2015, Li et al. induced ventricular fibrillation for 6 min followed by closed-chest compressions and IV administration of epinephrine and external defibrillator shocks until ROSC. [18F]FDG PET scans at baseline, 4, 24, and 48h after CA showed decreased cerebral glucose metabolism (CGM) decreased at 4h after ROSC and continued to remain lower than baseline up to 48h. Changes in CGM correlated with changes in hexokinase I and II expression measured by IHC6. Two studies in 2021 in mice measured increased glucose uptake 90min7 and 72h8 after cardiac arrest compared to baseline, suggesting an increased metabolic demand in the brain after severe neurological injury.

Although most studies have focused on global changes in glucose uptake and metabolism, some studies have reported brain regions susceptible in certain patient populations. A 2004 study by Frucht et al. noted patients who suffer from posthypoxic myoclonus tend to have significant increase in glucose metabolism in the ventrolateral hypothalamus and pontine tegmentum 9.

The utility of [18F]FDG and the use of SUVr as an early indicator of neurological outcomes shows promise in several studies. In rats with post cardiac arrest syndrome (PCAS), changes in SUV before and 3hr post PCAS induction were significantly lower in rats with good neurological outcomes compared to rats with poor outcomes measured with the Morris water maze test. Furthermore, forebrain-to-hindbrain SUVr was also a good predictor of outcomes10. In humans, significant differences in glucose uptake were seen between “good” and “bad” performers in patients with hypoxic-ischemic encephalopathy post cardiac arrest11.

## Regional cerebral blood flow and oxygen utilization

Studies using O-15 labeled radiotracers to evaluate regional cerebral blood flow (rCBF) and O2 metabolism mostly took place in the 2000s, mostly at Uppsala University in Sweden. Given the short half-life of 15O (t1/2=2.0min) compared to 18F-labeled compounds (t1/2 = 110min), several PET scans can be performed within a short time window. Furthermore, [15O]H2O shows better demarcation between white and gray matter regions compared to [18F]FDG12. In 2003, Edgren et al. were the first to show significant reduction in O2 metabolism measured as CMRO2 in comatose vs. recovered patients post cardiac arrest (N=7). These differences were most pronounced in the putamen and occipital cortex13.

In 2007, Mortberg et al. evaluated the temporal dynamics of rCBF shortly after cardiopulmonary resuscitation in 9 young pigs using [15O]H2O PET. They showed a drastic increase in CBF 10 min after resuscitation followed by cortical hypoperfusion and gradual return to baseline over the course of 4 hours14. Two years later, this same group measured perfusion/metabolism mismatch (CBF and CMRO2) and oxygenation extraction fraction (OEF). They showed preferential perfusion to the cerebellum and away from the telencephalon from 60-300 min, with changes in OEF that suggest a transition to ischemic state15.

## Evaluation of cardiac injury and prognosis

Cardiac PET has been used to evaluate several measures of cardiac function post cardiac arrest, including glucose metabolism with [18F]FDG, myocardial perfusion with [13N]ammonia, and ventricular denervation with [11C]-meta-hydroxyephedrine ([11C]HED).

The major focus in the use of cardiac PET has been to predict the risk of sudden cardiac death. Myocardial viability has been shown to be a better predictor of adverse cardiac events compared to the presence of scarring. For this reason, the Prediction of ARrhythmic Events with Positron Emission Tomography (PAREPET) was funded to use PET to evaluate several markers of cardiac function as a better predictive tool of adverse cardiac events16. Evaluation of PAREPET data in 2014 by Fallovollita et al. showed sympathetic denervation assessed using (11)C-HED PET predicts cause-specific mortality from SCA independently of LVEF and infarct volume17,18. Furthermore, [11C]HED was shown to have good test-retest reproducibility19. Despite evidence of denervation providing an improvement in predictions of sudden cardiac arrest compared to scarring, scarring still is a strong predictor in patients with LVEF < 35%20.

Preclinical studies are still in methodological development phase to assess myocardial ischemia. One challenge has been differences in myocardial injury depending on the method of SCA induction. In 2014, Wu et al. compared induction of SCA using ventricular fibrillation cardiac arrest (VFCA) vs. asphyxiation cardiac arrest (ACA) in 32 mini pigs. Using [18F]FDG, they found ACA induces more severe cardiac metabolism injuries compared to VFCA21. Finally, in 2018, Jiang et al. created a rabbit model to evaluate the influence of hydrogen intervention on myocardial metabolism. They found an increase in glucose uptake 2h and 24h after cardiac arrest, and this increase was blunted by hydrogen therapy22.

## Neuroinflammation post cardiac arrest

Little is currently known about neuroinflammation in the brain in the months following a cardiac arrest. Neuroinflammation is known to be mediated by cells that express the 18 kDa translocator protein (TSPO). The development of [18F]DAA1106 as a radioligand for specific binding to TSPO has been shown to be an excellent *in vivo* marker for neuroinflammation.

Only one study has evaluated neuroinflammation in post cardiac arrest setting. In 2021, Schroeder et al. studied five Sprague Dawley rats for 6 months post cardiac arrest and 3 sham rats, performing [18F]DAA1106 PET measurements on day 5, 8, 14, 90, and 180 after intervention. They showed bilateral accumulation of TSPO expressing cells in the dorsal hippocampus on all animals in all time points. TSPO expression negatively correlated with performance on the Barnes Maze test on day 14 and 18023.

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