^{11}C-acetate PET: A powerful tool to analyze metabolic and functional changes in the heart related to alcohol consumption

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Received Jun 19, 2020; accepted Jun 19, 2020
doi:10.1007/s12350-020-02268-0

See related article, pp. 278–288

''There can be economy only where there is efficiency''

Former British Prime Minister Benjamin Disraeli's commentary on efficiency may have relevance in the heart. In order to sustain life, the heart continuously converts chemical energy primarily from aerobic substrate oxidation to the vital mechanical energy that is used to pump blood throughout the body. The delicate balance of chemical input and mechanical output is upset in the failing heart, which is mired in a desperate and inefficient cycle of compensation to create sufficient mechanical work. Positron emission tomography (PET) with metabolic tracers such as ^{11}C-acetate, ^{11}C-glucose, ^{11}C-palmitate, $^{15}O_2$, and ^{18}F-fluorodeoxyglucose has significantly improved our understanding of the complex processes and adaptations involved in the progression of heart failure from its initial to advanced stages.[1,2] Coupling metabolic PET with functional imaging from echocardiography, magnetic resonance (MR), or gated or dynamic radionuclide imaging provides a metric of cardiac efficiency by comparing the external stroke work to the chemical energy used to create that work.[2] This analysis of cardiac efficiency has provided valuable perspectives on the energetic basis of heart failure and the mechanisms behind various treatments, such as inotropic stimulation,[3] neurohormonal blockade,[4] resynchronization,[5] and exercise training.[6] Moreover, measurements of myocardial efficiency have been shown to have powerful predictive value for cardiac death in patients with dilated cardiomyopathy.[7]

In the current issue of the *Journal of Nuclear Cardiology*, Shi et al. utilize ^{11}C-acetate PET and 2D echocardiography to compare the cardiac metabolic phenotypes of patients with alcoholic cardiomyopathy (ACM), asymptomatic individuals who chronically consume moderate and heavy amounts of alcohol, and healthy age-matched controls.[8] The authors present several important findings related to this analysis. First, they demonstrate that the estimated rate of myocardial oxygen consumption (MVO_2) was significantly reduced in patients with ACM and those with heavy alcohol consumption. On the other hand, k_{mono}, an index of the rate of myocardial O_2 consumption based on monoexponential curve fitting of ^{11}C-acetate washout, was significantly decreased in patients with heavy alcohol consumption and nonsignificantly decreased in those with ACM. In addition, myocardial external efficiency (MEE), a unitless ratio of external stroke work to energy produced by myocardial oxidative metabolism based on biexponential curve fitting of the ^{11}C-acetate washout curve, was significantly reduced in ACM, but preserved in moderate and heavy consumption. By comparison, a slightly different metric of efficiency, work metabolic index (WMI), which compares external stroke work to

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J Nucl Cardiol 2022;29:289–92.
1071-3581/$34.00

k_{mono}, was not significantly different between ACM, control, or moderate and heavy consumption patients. Lastly, the authors demonstrated that myocardial blood flow was not substantially altered by ACM or chronic alcohol consumption.

While these observations are interesting, some important limitations of the study should be mentioned up front. First, the study population did not include any female patients. This is highly relevant as there are known sex-related differences in alcohol processing and sensitivity that make females generally more susceptible alcohol-related cardiac damage.[9,10] Second, the findings specifically related to ACM need to be considered with caution, since this group was small (N = 5), and unlike the other groups, had documented dilated cardiomyopathies. In addition, three of the five ACM patients had discontinued alcohol consumption two to five years prior to the imaging studies.

Numerous groups have previously applied ^{11}C-acetate PET to study metabolic relationships in general populations with dilated cardiomyopathy (DCM).[3–6,11–14] To the best of our knowledge, the study by Shi et al. is the first to utilize ^{11}C-acetate PET to compare myocardial metabolism and function in specific populations with ACM and chronic asymptomatic alcohol consumption. While Shi et al. demonstrated a decrease in MVO_2 and a nonsignificant decrease in k_{mono} in the ACM population, prior studies of general DCM populations have yielded mixed results, with two showing decreased indices of myocardial oxygen consumption rates relative to controls[12,14] and one showing no difference.[11] Another study showed no difference in k_{mono} when compared to controls, but decreased rates of O_2 consumption relative to myocardial demand, as represented by k_{mono} divided by rate pressure product.[13] While DCM populations are characterized by left ventricular dilation and dysfunction, estimates of efficiency comparing stroke work per unit oxygen consumed are also typically decreased.[12] Ultimately, metabolic data for heart failure populations are inherently difficult to compare due to intrinsic heterogeneity that largely stems from the fact that common heart failure phenotypes such as DCM are often induced by multiple different pathological mechanisms. In addition, metabolic phenotypes in heart failure populations are dependent on the stage of disease and are further complicated by the effects of adaptive mechanisms and medical treatments.

In the work by Shi, et al., the finding of decreased MVO_2 in both ACM and heavy alcohol consumption may indicate a dose-dependent toxicity of alcohol and the presence of subclinical myocardial molecular dysfunction in asymptomatic individuals. The authors propose that the imaging biomarker MVO_2 could be used to discourage further alcohol consumption in patients with subclinical dysfunction who may be at risk for progression to ACM. While risk stratification is an important part of heart failure care, it seems rather unlikely that the information provided by the ^{11}C-acetate PET metabolic analysis would afford substantial additional motivation to addicted patients to cease or decrease alcohol consumption. However, the metabolic information may be useful for identifying asymptomatic individuals with alcohol use disorder who are at high risk for progression to heart failure and thus candidates for intensive cessation therapies. The presence of detectable structural and metabolic changes in the myocardium of asymptomatic patients with heavy alcohol consumption is further explored in a related article by these authors using cardiac magnetic resonance and ^{11}C-acetate PET/CT imaging.[15]

The significance of the disparate results for MEE and WMI in the ACM population is more complicated. While MEE and WMI both represent myocardial efficiency as indices of stroke work per unit O_2 consumed, there are several potentially significant differences between the two indices. For one, WMI was calculated with measurements of stroke work from 2D echocardiography, and MEE was calculated with values from dynamic ^{11}C-actetate PET imaging, using previously described and validated methods.[16,17] In addition, WMI utilizes systolic blood pressure to estimate stroke work and normalizes it to body surface area, while MEE utilizes mean arterial pressure and normalizes it to left ventricular mass. In addition, WMI utilizes k_{mono} as an index of the rate of myocardial O_2 consumption, while MEE relies on biexponential curve fitting of the ^{11}C-acetate washout curve to estimate absolute MVO_2, the rate of O_2 consumption per gram of myocardium. As a result, MEE is a unitless ratio and WMI has units of [mL·mmHg/m^2]. It is interesting to note that while the mean LVEF as calculated by echocardiography was significantly lower in ACM patients than normal controls (34% vs 65%, $P < 0.05$), echocardiographic stroke volume indices (stroke volume normalized to body surface area) utilized in WMI calculations were not significantly different. As noted above, however, the ACM group included only five patients, including three who ceased alcohol consumption years before the ^{11}C-acetate PET imaging study.

The myocardial oxygen consumption and efficiency measurements reported by Shi et al. were also likely affected to varying degrees by numerous differences between ACM patients and normal controls, including factors that are not directly related to the heart. For one, ACM patients had greater blood pressures and slower heart rates than the other groups. Hemodynamic factors such as preload and afterload have been previously demonstrated to significantly affect efficiency.[12] While

altered hemodynamics in the ACM group may directly result from cardiac dysfunction, it is also possible that there were additional influences from coexisting liver and/or kidney disease and the vasoactive influences of alcohol. In addition, the ACM group is likely to be treated with standard heart failure therapies such as neurohormonal antagonists and vasodilators, medications which may substantially affect MVO_2 and efficiency.[4] Furthermore, ACM is typically associated with increased myocardial mass. While eccentric hypertrophy in a dilated ventricle is a different phenotype than concentric hypertrophy related to increased afterload, prior studies demonstrate that concentric hypertrophy from hypertension is associated with preserved MVO_2, yet decreased efficiency.[18] Ultimately, basic mechanical factors related to ventricular dilatation and remodeling such as increased wall stress, sarcomere overextension, unfavorable geometry, fibrosis, and valvular regurgitation may also have significant effects on myocardial metabolism and performance. Factors such as valvular regurgitation and diastolic dysfunction related to hypertrophy or fibrosis tend to distort pressure–volume loops and can significantly affect noninvasive estimates of stroke work that approximate pressure–volume loops as rectangles.[2] The presence and severity of mitral regurgitation in ACM patients, as well as methods to account for this abnormality in stroke work calculations, are not described in the present study.[2]

Myocardial oxygen consumption and efficiency measurements may also be affected by differences in substrate availability and utilization. Alcohol use disorder is frequently associated with nutritional deficiencies and electrolyte derangements that could alter myocardial substrate utilization and affect function.[19] In addition, myocardial substrate utilization in the failing heart typically shifts towards greater utilization of glucose and lesser oxidation of free fatty acids.[11,20] This shift in substrate utilization can directly affect efficiency measurements as glucose yields more adenosine triphosphate (ATP) per O_2 than free fatty acids, but may eventually be detrimental to myocardial contractile function.[11,20] Moreover, questions have also been raised regarding the appropriateness of applying ^{11}C-acetate curve fitting analyses that were largely developed and validated in normal patients to those patients with advanced heart failure.[2]

The recent development of reliable methods to measure myocardial stroke work and oxidative metabolism from a single ^{11}C-acetate PET acquisition[16,17] is a major advancement for the field of metabolic imaging. This integrated approach can potentially improve the efficiency of imaging, with possible reductions in cost, acquisition time, and processing time. In addition, it eliminates previously unavoidable delays between the metabolic and functional acquisitions that could potentially influence results due to time-related changes in hemodynamic and other physiological variables. One factor that potentially limits the use of ^{11}C-acetate PET imaging is the relatively short half-life of ^{11}C and its dependence on cyclotron production. This underscores the need for the development of effective methods with alternative radiotracers that can be produced by onsite generators or delivered via distribution networks.

While metabolic analyses of heart failure are complex, they yield unique and useful data. ^{11}C-acetate PET is a valuable and underutilized technique for providing insight into the mechanisms of heart failure and related treatments. In an era of increased heart failure prevalence with a recent expansion of available treatments, there is now even greater potential value in robust tools for serial, noninvasive metabolic and functional analyses. For example, ^{11}C-acetate PET could be applied to improve understanding of the mechanisms of newer pharmacological heart failure therapies such as combined angiotensin receptor blockers/neprilysin inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists, as well as the many evolving forms of mechanical support. The current study presented by Shi et al. utilizes ^{11}C-acetate PET to compare the functional and metabolic states in patients who are asymptomatic and consume varying levels of alcohol to those with advanced ACM. The joint application of metabolic and functional imaging in these populations can potentially provide valuable information regarding risk stratification and may lead to better understanding of specific issues, such as male/female differences in ACM prevalence and alcohol dose dependency,[9,10] as well as the purported cardiovascular benefits of low to moderate levels of alcohol consumption.[21]

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