In Vivo Assessment of Myocardial Glucose Uptake by Positron Emission Tomography in Adults With the PRKAG2 Cardiac Syndrome

Andrew C.T. Ha, MD; Jennifer M. Renaud, MSc; Robert A. deKemp, PhD; Stephanie Thorn, MSc; Jean DaSilva, PhD; Linda Garrard, BScN; Keiichiro Yoshinaga, MD; Arun Abraham, MD; Martin S. Green, MD; Rob S.B. Beanlands, MD; Michael H. Gollob, MD

**Background**—The PRKAG2 cardiac syndrome is an inherited metabolic disease of the heart characterized by excessive myocardial glycogen deposition. The biochemical alterations associated with this condition remain controversial and have not previously been studied in affected humans.

**Methods and Results**—Positron emission tomography (PET) imaging was used to quantitatively assess myocardial glucose uptake (MGU) in 6 adult subjects with the PRKAG2 cardiac syndrome and 6 healthy, matched control subjects using the glucose analogue 18F-Fluoro-2-deoxyglucose (FDG). Studies were performed under a euglycemic hyperinsulinemic clamp to ensure stable blood glucose levels. Rubidium-82 perfusion scans were performed to ensure that myocardial differences in myocardial glucose uptake were not the result of significant myocardial scar. In adult patients with phenotypic expression of disease, the median myocardial glucose uptake of the left ventricle was 0.18 μmol/min/g (interquartile range, 0.14, 0.24), compared with 0.40 μmol/min/g (interquartile range, 0.30 to 0.45) in the control group (P=0.01). The median blood glucose during FDG-PET imaging was 4.72 mmol/L (interquartile range, 4.32 to 4.97) in the PRKAG2 group and 4.38 mmol/L (interquartile range, 3.90, 4.79) in the control group (P=NS). The significant decrease observed in myocardial glucose uptake in affected patients occurred in the absence of significant myocardial scar.

**Conclusions**—The PRKAG2 cardiac syndrome is associated with a reduction of glucose uptake in adult patients affected with this genetic condition. In this pilot study, 18F-FDG-PET imaging is a useful tool to assess alterations in myocardial glucose transport in this inherited metabolic disease and provide insight into the biochemical pathophysiology of the diseased state. (Circ Cardiovasc Imaging. 2009;2:485-491.)

**Key Words:** PRKAG2 ▪ positron emission tomography ▪ genetics ▪ cardiomyopathy

adenosine monophosphate-activated protein kinase (AMPK) is an important regulator of glucose and fatty acid metabolism in the human heart.2 AMPK activity is constitutive and is significantly augmented in response to increased myocardial energy demand, activating ATP-producing metabolic pathways through fatty acid oxidation and facilitating glucose uptake. Direct activation of AMPK activity is dependent on the AMPK γ-subunit, encoded by the PRKAG2 gene.2 Mutations of PRKAG2 result in a cardiac syndrome characterized by atrial fibrillation, ventricular preexcitation, progressive conduction system disease, and left ventricular (LV) hypertrophy.1,3-5 The central role of AMPK in regulating glucose metabolism had led to the hypothesis that the pathological basis of the PRKAG2 cardiac syndrome was due to impaired glucose metabolism and excessive glycogen storage.6-9 Subsequent histological studies of myocardial tissue from human subjects with the PRKAG2 cardiac syndrome confirmed excess glycogen stores in cardiac myocytes and a pathology distinct from more typical causes of cardiac hypertrophy secondary to hypertension or valvular heart disease.7,8

**Clinical Perspective on p 491**

The mechanism by which mutations of PRKAG2 leads to excess glycogen stores in the human heart is not well defined. Studies in transgenic mice expressing disease-causing human PRKAG2 mutations have provided conflicting results on measured AMPK activity, suggesting a “gain of function” in AMPK activity and enhanced glucose uptake throughout early disease stages6 or a “loss of function” in AMPK activity as measured during late disease.10 In humans, how glucose metabolism and AMPK activity are altered by disease-causing mutations of PRKAG2 remain unknown.

Myocardial glucose uptake (MGU) is regulated by AMPK.1,2,11 In humans, myocardial glucose uptake can be

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assessed by $^{18}$F-Fluoro-2-deoxyglucose dynamic positron emission tomography ($^{18}$F-FDG PET). Like glucose, FDG enters into myocytes via glucose transporters (GLUT-1 and GLUT-4) and is phosphorylated to FDG-6-phosphate by hexokinase. However, unlike glucose, FDG-6-phosphate is not further metabolized and is retained in myocytes. Thus, measurement of myocardial FDG activity reflects myocardial glucose uptake as well as the activity of hexokinase. Accordingly, we aimed to characterize myocardial glucose uptake activity using this quantitative imaging modality in human adults with the disease-causing R302Q mutation of PRKAG2.

Methods

Patient Population

Seven adult patients from a large extended family with an identified R302Q mutation of the PRKAG2 gene (PRKAG2) and 6 healthy adult volunteers (control) were recruited. All patients in the PRKAG2 group had phenotypic expression of the PRKAG2 cardiac syndrome. At the time of enrollment, 1 patient in the PRKAG2 group had progressed to dilated cardiomyopathy with severe LV dysfunction and was excluded from analysis. Patients in the control group had no known history of cardiac disease and were considered to have a low likelihood for coronary disease. No patients in either group had diabetes or impaired glucose tolerance. For all subjects, a detailed history, a 12-lead ECG, baseline blood work including fasting glucose, and resting arm blood pressure were obtained. This study was approved by the Research Ethics Board of the University of Ottawa Heart Institute, and all patients provided written informed consent for participation in the study.

PET Imaging: $^{82}$Rb PET Protocol

All patients underwent an overnight fast before the study. Patients were positioned in a whole-body PET scanner (ECAT ART; Siemens, Knoxville, Tenn), and a 4-minute $^{137}$Cs transmission scan was performed for attenuation correction. $^{82}$Rb (8 MBq/kg) was administered intravenously over 30 seconds immediately after the transmission scan, and a 7.5-minute acquisition was initiated 2.5 minutes after the start of $^{82}$Rb administration.

PET Imaging: $^{18}$F-FDG Protocol

A standard euglycemic hyperinsulinemic clamp was used. After an overnight fast, a 20-gauge polyethylene cannula was inserted into a superficial vein of the patient’s forearm for infusion of glucose and insulin. A second cannula was threaded retrogradely into a superficial vein of the hand on the opposite arm. This cannula was used for insulin. A second cannula was threaded retrogradely into a superficial vein of the patient’s forearm for infusion of glucose and insulin. A second cannula was threaded retrogradely into a superficial vein of the hand on the opposite arm. This cannula was used for insulin. A second cannula was threaded retrogradely into a superficial vein of the patient’s forearm for infusion of glucose and insulin. A second cannula was threaded retrogradely into a superficial vein of the hand on the opposite arm. This cannula was used for insulin.

PET Image Processing

$^{82}$Rb PET perfusion and $^{18}$F-FDG dynamic images of tracer activity over time were reconstructed using ECAT 7.2 software including attenuation and scatter correction. Filtered backprojection was used with a Hann window of the Ramp filter and a cutoff frequency of 0.35 cycles per pixel, resulting in 47 transaxial images per frame, with a spatial resolution of 12 mm in all 3 dimensions. To determine the myocardial activity over time, a custom program (FlowQuant) developed in our institution was used to automatically reoriented the images along the long axis of the heart and sample the LV myocardium into dynamic polar maps with 460 sectors, assuming a recovery coefficient value of 1.0. A cylindrical region was defined automatically within the LV and atrial cavities to determine the arterial blood-pool activity over time.

Data Analysis

The rate of myocardial glucose uptake in each polar map sector was calculated using the mathematical model developed by Patlak and Blasberg. This model defines the relationship between myocardial activity ($C_m(t)$) corrected for arterial blood-pool activity ($C_b(t)$) versus the integral of $C_b(t)$ corrected for the blood activity at that time $t$ ($\int C_b(t)dt/C_b(t)$). This relationship becomes linear after the transient response of tissue FDG (~5 minutes), similar to a constant FDG infusion. The slope of the linear portion of this relationship is equal to the net influx constant (Ki) of $^{18}$F-FDG, which represents the fractional rate of tracer uptake and phosphorylation. The rates of global and segmental MGU in the LV myocardium were calculated as (Ki/LC)×[glucose], where [glucose] was the average blood glucose level sampled during $^{18}$F-FDG PET imaging and the LC (lumped constant) value of 0.67 was used to correct for the differences in the transport and phosphorylation of $^{18}$F-FDG and glucose.

In this study, MGU was measured from dynamic FDG polar map data obtained from 0 to 40 minutes. Using the automated program, the LV polar map of MGU in each patient was divided into 17 segments according to standard criteria. Segmental MGU was calculated for each segment. The 17 segments were grouped into 3 levels: basal (6 segments), mid (6 segments), and apical (5 segments). Comparison of segmental MGU between the 2 groups was performed within each of the 3 levels.

Echocardiography

Two-dimensional and Doppler echocardiographic examinations were performed using the Sonos 5500 ultrasound system (Phillips, Andover, Mass). LV size, wall thickness, and LV mass were measured in accordance with recommendations from the American Society of Echocardiography.

Statistical Analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean±SD for normally distributed data and as median with interquartile ranges (IQR) for non-normal data. Categorical variables were analyzed using the Fisher exact test. Hypothesis testing of continuous variables was performed using Wilcoxon rank sum test. When segmental MGU comparison of the basal, mid, and apical levels of the LV polar map was performed, Bonferroni adjustment was applied by multiplying the unadjusted probability values by the number of comparisons made within each level. Correlation between variables was assessed with the Spearman rank correlation test. Statistical analysis was performed using SAS 9.1.3 (SAS, Inc, Cary, NC). Results were considered statistically significant at $P<0.05$.

Results

Patient Population

The baseline data for the 12 patients in the study are given in Table 1. The mean ages between the PRKAG2 and control groups were similar (39.3±16.5 years versus 34.2±9.7 years, $P=0.53$). No patients in either group had diabetes. Two patients in the PRKAG2 group had hypertension controlled with medications. All patients in the PRKAG2 group had ECG evidence of ventricular preexcitation and a history of supraventricular arrhythmias, with 5 patients having a history of atrial fibrillation. Three patients had permanent pacemak-
ers due to conduction disease and 1 patient had an implantable cardioverter-defibrillator due to a history of resuscitated ventricular fibrillation. Among the 3 patients with pacemakers, 2 patients were pacemaker-dependent and were ventricular-paced at the time of FDG-PET imaging.

Echocardiography
Echocardiographic data were available in 5 patients in the PRKAG2 group. The mean thickness of the interventricular septum was 16.3 ± 13.4 mm. One patient (patient 6) had a markedly thickened septum measured at 40 mm, with the inferolateral wall measured at 14 mm. The average inferolateral wall thickness was 11.6 ± 2.1 mm. The average LV mass was 127.0 ± 36.2 g/m². The average LV end-diastolic and end-systolic diameters were 47.0 ± 9.0 mm and 32.3 ± 10.5 mm, respectively. The LV ejection fraction was normal (≥55%) in all 5 patients.

82Rb Perfusion
82Rb PET perfusion images were obtained in 5 of 6 patients in the PRKAG2 group. One patient could not be scheduled for perfusion scanning and declined to return for repeat imaging. Perfusion images and polar maps of the 82Rb PET scans were constructed and were visually inspected regional uptake defects for evidence of scar. The 82Rb PET perfusion polar maps of 2 patients were completely normal. In 2 other patients, there was mild perfusion reduction at the apex consistent with apical thinning. The remaining patient (patient 6) had a mild perfusion defect in the basal to midanterior and anterolateral wall with apical sparing. The relative reduction of uptake in this patient’s 82Rb PET polar map was attributed to asymmetrical cardiac hypertrophy because this patient had a markedly thickened septum (40 mm).

Rates of MGU
Representative FDG-PET polar maps are shown in Figure 1. The median MGU of the LV in the PRKAG2 group was 0.18 μmol/min/g (IQR, 0.14, 0.24) compared with 0.40 μmol/min/g (IQR, 0.30, 0.45) in the control group (P = 0.01) (Figure 2). The median blood glucose during FDG-PET imaging was 4.72 mmol/L (range, 4.32, 4.97) in the PRKAG2 group and was 4.38 mmol/L (IQR, 3.90, 4.79) in the control group (P = NS). The MGU of each of the 17 myocardial segments was lower in the PRKAG2 group compared with the control group (Figure 3A through 3C). After adjustment for multiple comparisons, a statistically significant difference was noted in 4 segments between the 2 groups. We addressed whether a correlation existed between segmental wall thickness measured on echocardiography (basal anteroseptal and basal inferolateral walls) with the corresponding segmental MGU (Table 2). No statistically significant correlation was found between the basal anteroseptal wall and its corresponding MGU (Spearman ρ = 0.42, P = 0.30) and between the basal inferolateral wall and its corresponding MGU (Spearman ρ = 0.13, P = 0.76).

Discussion
In this study, FDG-PET imaging of adult patients with the PRKAG2 cardiac syndrome demonstrated decreased MGU compared with healthy adult subjects. The lower MGU observed in patients in the PRKAG2 group was not related to
any significant scar in the myocardium in which both FDG uptake and perfusion would be expected to be relatively reduced. Furthermore, regional analysis of the LV demonstrated that MGU was reduced in all major walls in adult patients with the R302Q mutation of \textit{PRKAG2}. These results indicate that a significant perturbation of myocardial glucose metabolism is observed in adult patients with overt phenotypic expression of the \textit{PRKAG2} cardiac syndrome, demonstrating decreased resting myocardial glucose uptake throughout the entire LV.

In adult human hearts, MGU is controlled by glucose transporters, predominantly GLUT-4. Glucose transport into myocytes is determined by the transmembrane glucose gradient and the quantity of glucose transporters at the cell membrane. During FDG-PET imaging, a steady serum glucose state is maintained with the euglycemic hyperinsulinemic clamp. Thus, the rate of transmembrane glucose transport should be primarily determined by the amount of glucose transporters present at the cell membrane. Therefore, the divergent MGU observed between the \textit{PRKAG2} and control groups probably is due to differences in membrane content of glucose transporters or alternatively may be limited by hexokinase activity, which phosphorylates FDG to FDG-6-phosphate, trapping the isotope within the myocyte.

The lower MGU in adult patients with the \textit{PRKAG2} cardiac syndrome appears paradoxical because cardiac hypertrophy caused by excessive glycogen storage is a hallmark of this condition. This apparent paradox may be explained by the developing nature of the disease process. It is recognized

\textbf{Figure 2.} Global LV myocardial glucose uptake. Box plot expresses MGU of the LV of patients in the \textit{PRKAG2} group and the control group.

\textbf{Figure 3.} A, Segmental MGU (LV, basal level). Box plot expresses MGU of the basal LV of patients in the \textit{PRKAG2} group and the control group. B, Segmental MGU (LV, midlevel). Box plot expresses MGU of the mid LV of patients in the \textit{PRKAG2} group and the control group. C, Segmental MGU (LV, apical level). Box plot expresses MGU of the apical LV of patients in the \textit{PRKAG2} group and the control group.
that the clinical features of this genetic syndrome are progressive, with worsening phenotypic expression over many years.\textsuperscript{3,4} In the early stages of disease development, MGU may indeed be elevated in the PRKAG2 cardiac syndrome, as suggested by measured AMPK activity in transgenic mice during early disease development.\textsuperscript{6} Presumably, enhanced AMPK activity is pivotal to the process of early myocyte glycogen accumulation by facilitating excessive cellular glucose uptake and subsequent storage to glycogen in the absence of metabolic demand. However, during later and more advanced stages of the disease in adulthood, AMPK activity may be suppressed by feedback mechanisms, resulting in the observed decrease in AMPK activity measured in adult mice with overt disease.\textsuperscript{10} Excess glycogen is known to exert a negative feedback mechanism on AMPK activity via the putative glycogen-binding domain within the $\beta$-subunit of AMPK.\textsuperscript{23–26} In the adult stage of disease in which excessive glycogen accumulation is present, AMPK activity may be downregulated through this mechanism, leading to loss of AMPK activity as observed in adult mice with advanced disease and explaining the apparent discordant findings reported on the effect of PRKAG2 mutations on AMPK activity in this genetic syndrome.\textsuperscript{6,10} In support of this hypothesis, Banerjee et al.\textsuperscript{27} reported biphasic AMPK activity in transgenic mice expressing the human T400N PRKAG2 mutation, demonstrating an increase of AMPK activity in mice at 2 days to 2 weeks of life and a decrease in AMPK activity in mice during adult life. In addition, increased AMPK activity was correlated to low cardiac glycogen content during the early disease stages, whereas diminished AMPK activity was observed when cardiac glycogen levels were high.\textsuperscript{27} Our study provided a snapshot of MGU, a surrogate of AMPK activity, in adult humans with well-developed clinical manifestations of the PRKAG2 cardiac syndrome and demonstrated significantly reduced MGU, which may be explained by decreased AMPK activity as predicted by studies in adult transgenic mice expressing this disease.\textsuperscript{10,27} The findings of this study are hypothesis-generating and may be useful in future studies evaluating the effect of altered AMPK activity and disease expression in humans with this genetic syndrome.

**Limitations**

FDG-PET imaging of patients with the PRKAG2 mutation can only examine the rate of myocardial glucose uptake. As such, the effects of altered AMPK activity on other key components of glucose metabolism, such as glucose oxidation and glycogen metabolism, cannot be studied. Further understanding of the balance between glycogenesis and glycogenolysis is critical in delineating the pathophysiologic mechanisms of excess cardiac glycogen accumulation. Furthermore, myocardial fatty acid metabolism is also affected by AMPK.\textsuperscript{28} How PRKAG2 mutations affect myocardial fatty acid metabolism and whether such changes in fatty acid metabolism affect glycogen stores remain undefined. These limitations highlight the important and complicated role of AMPK regulation on myocardial glucose and fatty acid metabolism and underscore the need to develop novel metabolic imaging agents to elucidate this complex network of metabolic pathways. Because echocardiographic measurements of wall thickness were not available in the control subjects, the same recovery coefficient was used to calculate MGU values for both the PRKAG2 and control subjects. Wall thickness in some PRKAG2 subjects was increased above normal, and this would tend to increase the mean MGU value in this group. Despite this potential confounding effect, a reduction in MGU values was still observed compared with the control subjects, although the magnitude may be underestimated. Last, although our data demonstrated the utility of FDG-PET imaging in assessing the metabolic perturbations of this genetic syndrome, the number of subjects in this study was small. Future studies with larger populations are required to validate the usefulness of PET imaging in this condition and similar metabolic cardiomyopathies.

**Study Implications**

The demonstration of reduced FDG uptake in patients with the PRKAG2 cardiac syndrome with FDG-PET imaging highlights the potential utility of this imaging modality in elucidating biochemical alterations of human metabolic disease. In the context of the PRKAG2 cardiac syndrome, severe hypertrophy on the basis of excess glycogen storage may mimic echocardiographic features seen in the more common genetic disease of hypertrophic cardiomyopathy.\textsuperscript{7} FDG-PET imaging may be helpful in distinguishing patients with cardiac hypertrophy caused by PRKAG2 mutations from those with hypertrophic cardiomyopathy. Among patients with HCM, myocardial FDG uptake had been shown to increase in hypertrophied segments,\textsuperscript{29} in contrast to the

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**Table 2. Segmental Wall Thickness and MGU of PRAKG2 Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Basal Anteroseptal Wall Thickness, $^a$ mm</th>
<th>Basal Anteroseptal MGU, $\mu$mol/min/g</th>
<th>Basal Inferolateral Wall Thickness, $^a$ mm</th>
<th>Basal Inferolateral MGU, $\mu$mol/min/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.0</td>
<td>0.38</td>
<td>12.0</td>
<td>0.42</td>
</tr>
<tr>
<td>2</td>
<td>7.6</td>
<td>0.15</td>
<td>10.0</td>
<td>0.15</td>
</tr>
<tr>
<td>3</td>
<td>8.9</td>
<td>0.24</td>
<td>8.9</td>
<td>0.29</td>
</tr>
<tr>
<td>4</td>
<td>...</td>
<td>0.24</td>
<td>...</td>
<td>0.34</td>
</tr>
<tr>
<td>5</td>
<td>13.0</td>
<td>0.17</td>
<td>13.0</td>
<td>0.17</td>
</tr>
<tr>
<td>6</td>
<td>40.0</td>
<td>0.09</td>
<td>14.0</td>
<td>0.09</td>
</tr>
</tbody>
</table>

$^a$ No statistically significant correlation exists between basal anteroseptal wall thickness and its corresponding MGU (Spearman $\rho = -0.42, P = 0.30$).

$^a$ No statistically significant correlation exists between basal inferolateral wall thickness and its corresponding MGU (Spearman $\rho = -0.13, P = 0.76$).
significant reduction observed in our series of PRKAG2 patients. Finally, serial imaging of patients with the PRKAG2 cardiac syndrome with FDG-PET may be of potential value in monitoring disease progression.

Conclusion
Using FDG-PET imaging, we showed that PRKAG2 adult patients with advanced phenotypic expression of the PRKAG2 cardiac syndrome have reduced MGU when compared with normal control subjects. The reduction of MGU appears to affect the entire LV.

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Disclosures
None.

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**CLINICAL PERSPECTIVE**

Metabolic cardiomyopathies may mimic more common forms of myocardial disease such as hypertrophic cardiomyopathy but have distinct biochemical abnormalities that lead to the diseased phenotype. Radiotracer positron emission tomography imaging presents a novel methodology of studying abnormalities in metabolic pathways using in vivo studies in humans affected with such conditions. Gaining an understanding of the biochemical alterations in vivo provides an opportunity to consider specific pharmacological interventions that may alter cellular biochemistry to attenuate or reverse disease. Further, serial studies using the appropriate metabolic tag may be useful in monitoring disease progression or response to therapies. This pilot study highlights the utility of Fluoro-2-deoxyglucose–positron emission tomography imaging in the study of the PRKAG2 cardiac syndrome, a metabolic disease of the heart characterized by abnormalities in glucose metabolism.
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