Enhanced Myocardial $^{18}$F-2-Fluoro-2-Deoxyglucose Uptake After Orthotopic Heart Transplantation Assessed by Positron Emission Tomography

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Objectives. We sought to assess the relation between glucose metabolism, myocardial perfusion and cardiac work after orthotopic heart transplantation.

Background. The metabolic profile of the transplanted cardiac muscle is affected by the lack of sympathetic innervation, impaired inotropic function, chronic vasculopathy, allograft rejection and immunosuppressive therapy. In relation to myocardial perfusion and cardiac work, glucose metabolism has not previously been studied in heart transplant recipients.

Methods. Regional myocardial blood flow (ml/min/g) and $^{18}$F-2-fluoro-2-deoxyglucose ($^{18}$FDG) uptake rate (ml/s/g) were measured after an overnight fast in 9 healthy male volunteers (mean age ± SD 32 ± 7 years) and in 10 male patients (mean age 50 ± 10 years) who had a nonrejecting heart transplant, normal left ventricular function and no angiographic evidence of epicardial coronary sclerosis. Measurements were made by using dynamic positron emission tomography (PET) with $^{15}$O-labeled water and $^{18}$FDG, respectively. Heart rate and blood pressure were also measured for calculation of rate-pressure product.

Results. $^{18}$FDG uptake was similar in all heart regions in the patients and volunteers (intrasubject regional variability 12 ± 8% and 16 ± 12%, respectively, p = 0.51). Regional myocardial blood flow was similarly evenly distributed (intrasubject regional variability 14 ± 10% and 12 ± 8%, respectively, p = 0.67). Mean $^{18}$FDG uptake and myocardial blood flow values for the whole heart are given because no regional differences were identified. $^{18}$FDG uptake was on average 196% higher in the patients than in the volunteers (2.90 ± 1.79 × 10⁻² vs. 0.98 ± 0.38 × 10⁻² ml/s/g, p = 0.006). Regional myocardial blood flow and rate-pressure product were similarly increased in the patient group, but by only 41% (1.14 ± 0.3 vs. 0.81 ± 0.13 ml/min/g, p = 0.008) and 53% (11,740 ± 2,830 vs. 7,689 ± 1,488, p = 0.001), respectively.

Conclusions. $^{18}$FDG uptake is homogeneously increased in normally functioning nonrejecting heart transplants. This finding suggests that glucose may be a preferred substrate in the transplanted heart. The magnitude of this observed increase is significantly greater than that observed for myocardial blood flow or cardiac work. In the patient group, the latter two variables were increased to a similar degree over values in control hearts, indicating a coupling between cardiac work load and myocardial blood flow. The disproportionate rise in $^{18}$FDG uptake may be accounted for by inefficient metabolic utilization of glucose by the transplanted myocardium or by the influence of circulating catecholamines, which may stimulate glucose uptake independently of changes in cardiac work load.

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Under physiologic conditions the heart is an aerobic organ with free fatty acid representing the major metabolic substrate (1–3). After heart transplantation, although rest cardiorespi-
perfusion reserve of the transplanted heart (16,17). Drake-Holland et al. (18) showed that glucose oxidation was significantly reduced in comparison with other substrates in auto-transplanted baboon hearts, attributing these observations to disruption of the extrinsic autonomic innervation of the heart. In human cardiac allograft recipients, factors in addition to chronic denervation may influence myocardial glucose metabolism. These include 1) increased cardiac work load due to the combination of increased heart rate (owing to loss of vagal tone) and increased circulating catecholamine levels (8,16,17,19), and cyclosporine-induced hypertension (20); 2) accelerated coronary vasculopathy (21); and 3) allograft rejection (22).

Thus, in this study, we assessed myocardial glucose uptake in vivo in 10 fasting patients with a nonrejecting cardiac allograft and in 9 healthy human volunteers. Our studies used PET scanning and the glucose analog $^{18}$F-2-fluoro-2-deoxyglucose ($^{18}$FDG) on the assumption that this variable gives direct evidence of the glucose metabolic state in human cardiac allografts.

### Methods

#### Study group

Ten male nondiabetic orthotopic heart transplant recipients, ranging in age from 29 to 62 years (mean ± SD 50 ± 10) were selected for this study. Before transplantation, eight patients had had end-stage heart disease due to ischemic heart disease and two had had idiopathic dilated cardiomyopathy. Tomographic studies were carried out 13 to 60 months (34 ± 14 months) after transplantation. All patients had neither a history nor physical findings consistent with heart failure and had normal cardiac function on ventriculography and electrocardiographic findings compatible with post-transplantation myocardial infarction.

Nine male volunteers with an average age of 32 ± 7 years were recruited to construct a normal $^{18}$FDG uptake and myocardial blood flow data base. None had previous symptoms, signs or ECG evidence of heart disease. None was taking any medications.

Informed written consent was obtained from each patient. The study protocol was approved by the Hammersmith and Harefield Hospital Research Ethics Committees and the Administration of Radioactive Substances Advisory Committee (UK).

#### Scanning procedures

All subjects were studied after an overnight fast. Apart from the immunosuppressive agents, all medication was withheld 48 h before the tomographic study in the transplant group. Imaging was performed with a multislice ECAT 931/08-12 tomograph (CTI Inc.). Further details on the physical performance of this scanner have been reported elsewhere (23).

Each subject was first positioned within the scanner for a 5-min rectilinear transmission scan to allow optimal positioning of the heart in the center of the field of view of the camera. A 20-min transmission scan was then performed by the exposure of an external $^{68}$Ge ring source. These data were used to correct subsequent emission scans for tissue attenuation of the 511-keV gamma photons. This scan was followed by an oxygen-15-labeled carbon monoxide blood volume scan, as previously described (24). When activity had decayed to background levels, myocardial blood flow was measured by using oxygen-15-labeled water ($H_2^{15}O$) delivered by the inhalation of oxygen-15-labeled carbon dioxide ($C^{15}O_2$). Scanning procedures and myocardial blood flow data analysis have been reported previously in detail (24). After a 15-min interval to allow for decay of oxygen-15 radioactivity, $^{18}$FDG (185 MBq) was infused intravenously over 2 min. A 36-frame dynamic scan was started 30 s before the start of $^{18}$FDG infusion, thus enabling measurement of residual background activity. This scan lasted for 65 min. In all subjects, venous blood samples for plasma glucose were obtained before the scan to ensure fasting conditions. The rate-pressure product (heart rate times systolic blood pressure) was obtained during the image acquisition.

#### Data analysis

The emission data collected by the scanner were corrected for tissue attenuation and reconstructed into images with an inplane spatial resolution of 8.4 mm full width at half maximum (FWHM) and a slice thickness of 6.6 mm FWHM. These images were transferred to SUN 3/60 workstations (Sun Microsystems) for further image processing using the Analyze (Mayo Foundation) software package (25) and kinetic analysis using the MatLab mathematical software package (The MathWorks Inc.).

#### Definition of regions of interest

Vascular regions of interest were defined on the quantitative images of blood volume, as previously described (24,26). A mean of four left atrial regions with an average size of 100 pixels (~4 cm$^2$) and recovery coefficients >90% were selected. These were then
projected onto the dynamic H215O and 18FDG frames, thereby creating left atrial time-activity curves for each tracer. The average of these curves was used as arterial input function for the calculation of myocardial blood flow and 18FDG uptake. Tissue regions of interest of 5-pixel radius (equivalent to a 10-mm radius) were positioned in the four anatomic segments of the myocardium (anterior, lateral, inferior and septum). These were identified on each slice of the extravascular tissue density images (D
z
; g total [anatomic] tissue per ml region of interest), created by subtracting images of blood density from the corresponding transmission images after normalization of the latter to tissue density (27). Tissue regions of interest were then projected onto the dynamic H215O data set and onto the last 10-min 18FDG data acquisition frame, recorded during the period 55 to 65 min after the start of tracer administration, to generate tissue time-activity curves for the four myocardial segments. For each segment, the average regional H215O time-activity curve was used to estimate myocardial blood flow. Consistency of the vascular and tissue regions of interest was checked on the H215O images and the 18FDG images to ensure no significant patient movement during the scanning procedures.

Calculation of regional myocardial blood flow and 18FDG uptake. The vascular and tissue time-activity curves obtained from the C15O2 inhalation blood flow study were fitted to a single-tissue compartment tracer kinetic model as previously described (24,26). This model incorporates correction for 1) the underestimation of tissue activity due to cardiac wall motion and the small transmural myocardial thickness relative to the spatial resolution of the scanner, and 2) the fractional spillover of activity from the left ventricle into the tissue regions of interest.

With the use of the average of the left atrial 18FDG time-activity curves, the area under the curve of the arterial input function was calculated. The tissue regions of interest were projected onto the last frame of the dynamic 18FDG data set. This procedure allows determination of the accumulation of 18FDG in the different regions of the left ventricle. Regional 18FDG uptake (rFDGU; ml s−1·ml ROI) was defined as the ratio between the average 18FDG pixel counts in the tissue regions of interest to the integral of the arterial input function:

\[ r_{\text{FDGU}} = \frac{C_{\text{m}(T)}}{\left( \int_0^T C_{\text{a}(t)} \, dt \right)} \]

where \( C_{\text{m}(T)} \) represents the mean FDG activity (counts s−1·pixel−1) in the tissue regions of interest during the last frame of the 18FDG scan and \( C_{\text{a}(t)} \) (counts s−1·pixel−1) represents the left atrial input function (28–30). Regional 18FDG uptake values were corrected for partial volume effects by normalizing to tissue fraction (\( t_e \), ml exchangeable tissue per ml region of interest) (27) and converted from units of ml s−1·ml−1 to ml s−1·g−1 by further dividing by the density of myocardial tissue (1.04 g ml−1).

Statistical methods. Data were expressed as mean value ± SD. Statistical analysis was performed by using the Student’s t test; multiple data sets were compared by analysis of variance (ANOVA). If significant differences were found, post hoc pairwise intergroup comparisons were performed by the adjusted t test within ANOVA (least significant difference test). Correlation of coefficients was calculated with the least-squares linear regression analysis. A p value < 0.05 was considered significant.

Results

Clinical and tomographic data are summarized in Table 1. Heart rate, systolic arterial pressure, rate-pressure product, regional myocardial blood flow and regional 18FDG uptake data were compared between the two groups. Rest heart rate, systolic blood pressure and rate-pressure product were 25%, 24% and 53%, respectively, higher in the patients than in the normal subjects (p = 0.006, 0.001 and 0.001, respectively).

Regional myocardial blood flow. In both groups, myocardial blood flow was homogeneously distributed in the four left ventricular regions (anterior, lateral, inferior and septum). Mean intrasubject regional variability was 14 ± 6% in the transplant patients and 12 ± 8% in the normal volunteers (p = 0.67). Mean regional myocardial blood flow was 41% higher in the patients than in the volunteers (1.14 ± 0.3 vs. 0.81 ± 0.13 ml·min−1·g−1, p = 0.008). Mean values of perfusible
Myocardial metabolism, perfusion autoregulation and receptor-mediated cardiac responses of the orthotopic heart transplant have gained increasing attention in the last few years (10,16,17,19). Metabolic and perfusion alterations in the transplanted human heart have been related to several factors: the higher metabolic need of the transplanted heart compared with that of the normal heart; the effects of chronic denervation and heart responsiveness to neurotransmitter compounds; hormonal and circulating catecholamine changes after transplantation; coronary vasculopathy; and chronic rejection and immunosuppressive therapy. It has been suggested that patients with a transplanted heart are likely to function in a state of myocardial metabolic inefficiency. These factors will be discussed in greater detail later.

Pathogenesis and significance of $^{18}$FDG findings. The homogeneous increase in regional glucose uptake observed in transplant recipients reflects an increased transmembrane transport and phosphorylation of exogenous glucose, as the phosphorylated compound $^{18}$FDG-6-phosphate cannot be metabolized further. It is trapped within the cell in proportion to the uptake and phosphorylation of exogenous glucose because of its hydrophilic structure and its extremely slow myocardial clearance (31,32). Therefore, these data give no indication as to the ultimate metabolic fate of glucose in the transplanted heart. Several hypotheses may explain the observation of enhanced glucose uptake in transplants.

Metabolic demand. Increased cardiac work load may explain the increment in glucose uptake in the transplanted heart. Studies in the isolated rat heart (33) have shown that substrate utilization, in particular glucose, is related to the degree of myocardial loading. Furthermore, such high work load conditions may result in myocardial hypertrophy, which may also explain a relatively enhanced glucose uptake in the transplanted human heart. This has been demonstrated in habitually pressure-overloaded normal hearts and is associated with decreased free fatty acid analog extraction (33–36). Hypercontractility may also lead to an increase in carbohydrate utilization, as shown in patients with coronary artery disease (37,38) and in isolated pig hearts (39). Therefore, in the transplanted, normally functioning heart, enhanced glucose uptake may be secondary to the high work load conditions under which the heart operates.

Adrenergic mechanisms. Both alpha- and beta-adrenergic mechanisms appear to be involved in the control of glucose uptake by way of increasing cardiac contractility (40,41) and activation of phosphofructokinase, the rate-limiting enzyme of cardiac muscle glycolysis (42). Both adrenergic control of glucose uptake and phosphofructokinase activity are calcium dependent and influenced by alpha- and beta-adrenergic receptor mechanisms. Glucose uptake may be influenced not only by alterations of circulating catecholamines, but also by late cardiac sympathetic reinnervation and local release of catecholamines from sympathetic neurons (8,43,44), ultimately leading to a disproportionate rise in glucose uptake. In addition, as denervation is known to alter tissue adrenoceptor density, it may be speculated that “up-regulation” of beta-
adrenergic receptor stimulation and a hypersensitivity to beta- 
adrenergic receptor stimulation, as shown in vitro studies (45), may contribute to enhanced glucose uptake in the 
transplanted heart. However, in myocardial tissue specimens 
from clinically stable heart transplant recipients, neither beta-adrenergic receptor density nor the response of \[\text{adenylate cyclase to isoproterenol} \] differs from that in normal myocardium (46). A more recent study (47) has shown that \[\beta_2\] receptors are increased in transplanted human ventricles whereas the total beta-adrenergic receptor density is un-
changed, resulting in a lower \[\beta_2\]/\[\beta_1\] receptor density ratio (47). Thus, although upregulation of beta receptors 
mediating the increase in glucose uptake is a teleologically 
attractive hypothesis, supporting evidence is at present equivocal.

Coronary vasculopathy. Another possible explanation is 
that myocardial blood flow to the human transplanted myocar-
dium is not proportionally increased to meet the higher 
metabolic need of the transplanted heart. It is conceivable that 
the myocardium suffers from a chronically inadequate coupling 
of blood supply and metabolite requirement, resulting in a 
high “demand ischemia.” Thus the myocardium may be un-
derperfused, not in terms of absolute blood flow but in relation 
its higher metabolic requirement. This imbalance may be
enough to create a consistent metabolic shift of the whole 
heart toward an increased glucose utilization, which then 
becomes the main fuel source for the transplanted heart. In 
contrast to the ischemic heart, where compromised perfusion has long been equated with an increased glucose uptake in the 
distribution territory of the ischemia-related vessel (28,38), the 
inadequate perfusion-autoregulation coupling in the individual 
transplanted heart appears not to be sufficiently critical to be 
detectable with conventional perfusion agents unless a concur-
rent, rapidly developing coronary vasculopathy is superim-
posed. However, it may be sufficient to act as a potent substrate 
modifier, causing enhanced glucose uptake. In this respect, it is 
noteworthy that the presence of metabolic ischemia may occur 
without detectable perfusion abnormalities under conditions 
of increased cardiac work load (48,49).

In this group of cardiac allograft recipients, neither wall 
motion abnormalities nor significant epicardial coronary les-
sions were demonstrable. Myocardial blood flow was homoge-
neously distributed and in the range reported for healthy volunteers (50). Thus, myocardial ischemia, including silent ischemia, is unlikely to account for the raised uniform regional 
\[\text{18FDG uptake observed in the heart transplants.} \]

Metabolic aspects. Uptake and use of a given substrate by the 
myocardium depends on a variety of factors, including 
substrate availability, hormonal status, cardiac work load and 
the presence and severity of myocardial ischemia. In the fasting 
state, when plasma glucose levels are reduced and insulin levels 
are low, the normal myocardium utilizes relatively little 
glucose. The transplanted heart, operating at a higher demand 
level, may consume relatively more glucose as a result of 1) a 
reduced or insufficient availability of free fatty acids or, 
alternatively, 2) a saturation or ineffectiveness of the beta-
oxidative pathway; 3) altered hormonal activity; 4) chronic 
rejection; or 5) immunosuppressive therapy. In this context, it 
has been demonstrated (34) that a decline in free fatty acid 
concentration and an increase in glucose and insulin levels result in a high uptake of \[\text{18FDG in normal myocardium and in} \] moderately injured, ischemic myocardium. Little is known 
about the progression of metabolic derangement that may reflect the duration of cyclosporine therapy and the metabolic 
aspects of acute or chronic allograft rejection. Glucose may be 
a preferred metabolic substrate during acute rejection, as 
shown by Hoff et al. (22) in a nonworking experimental model. 
In our group of transplant recipients, it is more likely that the 
disproportionately high \[\text{18FDG uptake in relation to cardiac} \] work load and myocardial perfusion may represent decreased 
metabolic efficiency of the transplanted myocardium (10); that 
is, a greater amount of substrate needs to be utilized to generate 
a given level of contractile performance, and or, a chronic 
adaptation of myocardial metabolism to a situation of persistent 
high work load conditions in the presence of raised circulating 
catecholamine levels and or myocardial norepinephrine release, 
resulting in altered patterns of substrate utilization.

Conclusions. The present study shows an increase in 
\[\text{18FDG uptake in nonrejecting orthotopic transplanted hearts,} \] which suggests increased glucose metabolism in these patients. 
These findings suggest that glucose may be a preferred sub-
strate in heart transplants. Furthermore, as the increment in 
\[\text{18FDG uptake is disproportionately high compared with the} \] increments in cardiac work load and myocardial perfusion, this 
functional-metabolic uncoupling may indicate a decreased 
efficiency of glucose utilization or a stimulation of glucose 
uptake by raised circulating catecholamine levels, which stim-
ulate glucose uptake in the chronically denervated trans-
planted heart independently of cardiac work load. Further 
studies of substrate utilization under tightly fixed metabolic 
conditions, such as the euglycemic hyperinsulinemic clamp 
(51), and the relation between myocardial metabolism and 
contractile function in heart transplants are warranted.

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