Evidence of reverse mismatch with positron emission tomography imaging in a patient with reversible myocardial dysfunction

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We describe the case of a patient who came to our attention because of a reversible depression of myocardial contractility, probably due to myocarditis. A positron emission tomography study showed, in correspondence to the malfunctioning segments, a decreased F18-2-fluoro-2-deoxyglucose (F18-FDG) uptake in the presence of a normal perfusion as assessed by means of N13-labeled ammonia uptake. This phenomenon, called "reverse mismatch", shows that viability is not always dependent on FDG uptake and that it could be associated with the recovery of myocardial contractility. Some interpretations of the association between a reversible dysfunction and a reduced myocardial glucose metabolism are presented. The central role of nitric oxide and of cyclic guanosine monophosphate is hypothesized to explain both the mechanical and metabolic abnormalities.

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Introduction

Positron emission tomography (PET) is a powerful experimental and clinical tool for the simultaneous assessment of both the perfusion and metabolic function of the myocardium. The most widely used tracer for the evaluation of cardiac metabolism is F18-2-fluoro-2-deoxyglucose (F18-FDG), while N13-labeled ammonia (N13-NH3) is commonly used to measure the myocardial blood flow. A pattern of match or mismatch between myocardial metabolism and flow is obtained from the combination of possible variations in the uptake of N13-NH3 and of F18-FDG. A typical mismatch is observed in hibernated and viable myocardium, where the reduced flow is associated with a normal or relatively increased glucose uptake[1]. Otherwise, the presence of an atypical reverse mismatch, i.e. a normal myocardial flow with a reduced F18-FDG uptake, has been sometimes reported in ischemic disease[2,3] and in the septum of patients with left bundle branch block[4,5].

In this paper, we describe the presence of the same reverse mismatch pattern between glucose uptake and perfusion in a patient with a reversible myocardial dysfunction.

Case report

A 62-year-old woman presenting with prolonged chest pain lasting 8 hours and raised serum myocardial enzymes was admitted to the Interventional Coronary Unit. The ECG showed normal sinus rhythm and aspecific repolarization abnormalities. The patient's history included systemic hypertension and hypercholesterolemia. On admission the woman was slightly febrile; otherwise, the patient's physical examination, blood pressure and chest X-ray were normal; a transthoracic echocardiographic examination showed a mildly dilated left ventricle with widespread akinesia of all the midapical segments, a severely depressed global function and mild pericardial effusion. Biochemical analysis showed, during the first 24 hours, constant but slightly increased serum levels of myocardial enzymes and of the C-reactive protein (0.9 mg/dl) and an elevated erythrocyte sedimentation rate (44 mm/hour at the first hour).

On the second day a PET study was performed using a scanner Ecat Exact (model 921, CTI-Siemens, Knoxville, TN, USA). At first, a transmission scan of 15 min was obtained using retractable 68G rod sources for the correction of attenuation. For the

emission studies, the tracers used were N13-NH3 (dose 10 MBq/kg), injected at rest, and F18-FDG (dose 4 MBq/kg), injected after an oral glucose load coupled with intravenous insulin according to the suggestions of Lewis et al.[6]. Short-axis, vertical and horizontal long-axis slices, with a thickness of 0.8 cm each, were reconstructed using a Hanning filter (cut-off 1.18 cycles/cm). Both examinations were performed on the same day, first the N13-NH3 study, and 2 hours later the F18-FDG study. To avoid artifacts due to misalignment, the repositioning of the patient in the scanner was checked using a cross-shaped low-power laser beam and pen skin markers. Semiquantitative analysis of the images was performed by the consensus of two skilled observers. The four walls of the left ventricle (anterior, lateral, inferior and septum) were each divided into three equally sized segments (basal, midventricular and apical) for a total of twelve segments. After individual normalization of each set of images to the maximum count in the left ventricular wall, a three-point semiquantitative score was applied both for the F18-FDG as well as for the N13-NH3 images: 2 = normal uptake (> 75%), 1 = moderate defect (50-75%), 0 = severe defect (< 50%). A reversed mismatch was considered present in the segments presenting an F18-FDG score inferior to the corresponding N13-NH3 score.

As may be clearly seen in figures 1 and 2, the study highlighted a mismatch, in view of the presence of a severely defective F18-FDG uptake in all midapical segments in concomitance with a normal perfusion.

In the following days the ECG changed, with the appearance of negative T waves. The only relevant clinical event was the development of atrial fibrillation on the third day, with a rapid restoration of sinus rhythm following the infusion of cordarone. The coronary angiogram was completely normal. Viral serology and immunologic markers were negative. In the absence of histological confirmation by myocardial biopsy, a definitive diagnosis was not possible, but in the absence of other possible causes of myocardial dysfunction, myopericarditis seemed to be the most likely diagnosis.

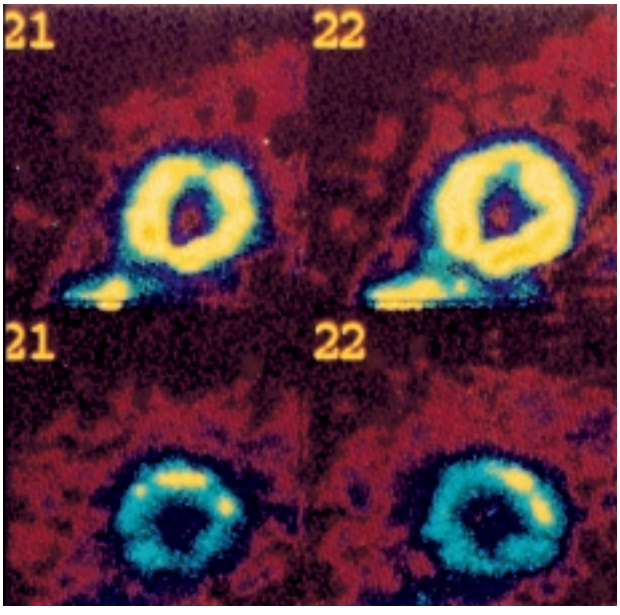

Figure 1. *Positron emission tomography of short-axis slices. The images* at the top *represent the perfusion study: the normal distribution of the tracer is evident. The images* at the bottom *represent the metabolic study: a markedly reduced metabolism as assessed by F18-2-fluoro-2-deoxyglucose uptake is present.*

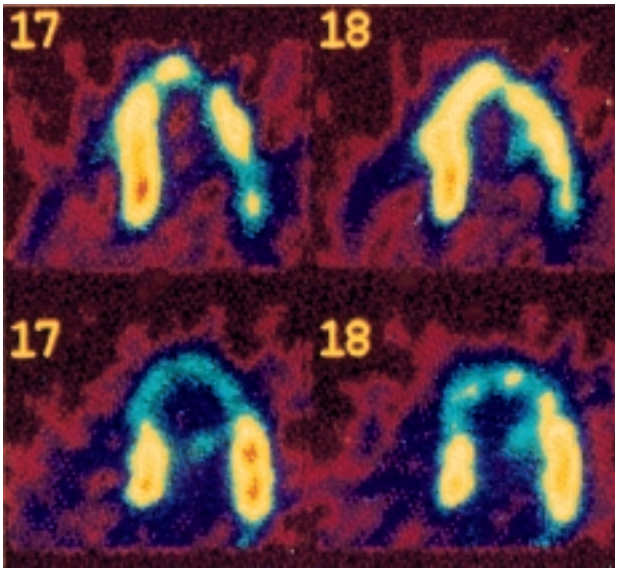

Figure 2. *Positron emission tomography of horizontal long-axis slices, corresponding to an echographic 4-chamber view. The images* at the top *represent myocardial perfusion and the images* at the bottom *represent the metabolic study: a clear mismatch between a homogeneous perfusion and a reduced F18-2-fluoro-2-deoxyglucose uptake may be observed in the midapical segments.*

Serial echographic examinations showed a progressive improvement in ventricular kinetics, with a complete normalization at 1 month of follow-up. After 6 months of follow-up, myocardial kinetics was still normal and a new PET study showed normal myocardial perfusion and glucose uptake (Figs. 3 and 4).

Discussion

The term "reverse mismatch" has been introduced to describe the pattern of a decreased F18-FDG uptake relative to the myocardial blood flow. It has been reported in limited numbers of patients with documented coronary disease and early after acute myocardial infarction[2,3], and in some cases of patients with left bundle branch block[4,5]. This phenomenon may seem quite paradoxical since the decrease in glucose metabolism occurs in concomitance with a normal myocardial blood flow.

This report has highlighted that a reverse mismatch may also occur in patients with reversible myocardial dysfunction. The putative diagnosis in our patient was that of myopericarditis, but we think that the central point is the possible association between the abnormal-

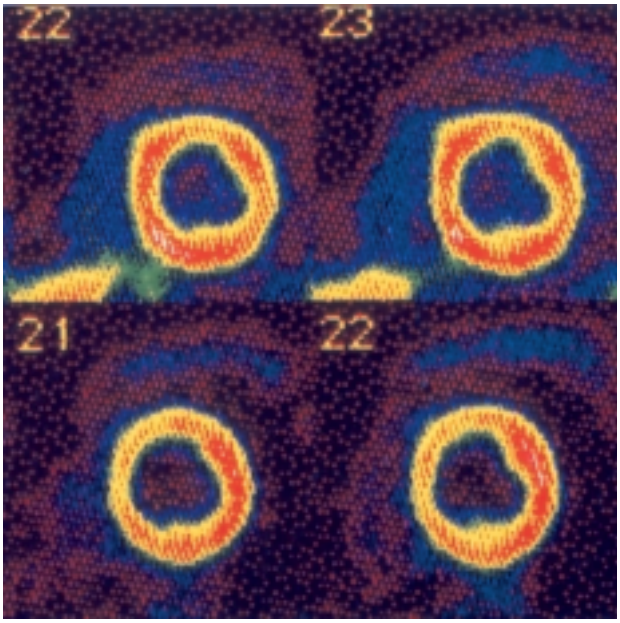

Figure 3. *Short-axis views as in figure 1 on follow-up: normalization of F18-2-fluoro-2-deoxyglucose uptake.*

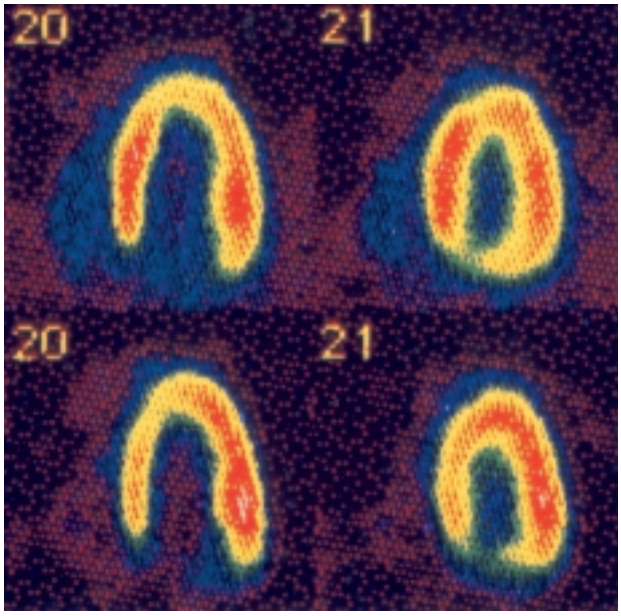

Figure 4. *Horizontal long-axis views as in figure 2 on follow-up: normalization of F18-2-fluoro-2-deoxyglucose uptake.*

ities in glucose metabolism in the presence of normal perfusion and of reversibly depressed contractility, whatever the cause of myocardial dysfunction may have been. Anyway, alterations in single-photon emission computed tomography tracer uptake have already been described in myocarditis, raising the possibility of a reversible abnormality in myocardial metabolism and of a dysfunction of the cardiac sympathetic nerve supply[7,8].

The PET image is a reproduction of particular functions of a structure, and first of all we must determine whether the information obtained is distorted, i.e. whether what we see is real or not. This technique has a good spatial resolution, and allows for the correction of photon attenuation and of partial volume effects. Despite these features, the apparently reduced glucose uptake could still be an artifact, because PET does not completely correct the partial volume effect. In nuclear medicine the total counts in a volume are influenced by this effect, which consists of the process of averaging when pixels encompass more than one adjacent tissue such as the myocardium and ventricular cavity. As a result, the net intensity of the pixel is determined by the relative proportion and signal intensity of each component. According to partial volume averaging, the changes in the myocardial wall motion are reflected as changes in the pixel counts representing the myocardial wall. However, this effect should be equally present in both perfusion and metabolic acquisitions, and, for this reason, it does not explain the discrepancy between studies.

Technical artifacts due to misalignment also seem unlikely since, as already described, the repositioning of the patient was carefully checked.

The particular plurisegmental and circumferential decrease in glucose metabolism is not compatible with the regional heterogeneity of the cardiac substrate metabolism already described in some conditions[9].

A limitation was the semiquantitative analysis of FDG and NH3 uptake, since the absolute determination of glucose uptake was not estimated. For this reason, a relatively decreased FDG uptake in the midapical segments might actually be suggestive of a relatively increased glucose consumption in the proximal segments, in the presence of a possible inflammatory strain infiltrating the basal myocardium and causing a higher glucose consumption. But this would be in contrast with the perfect matching between the segmental depression of contractility and the decreased glucose uptake in the midapical segments, i.e. the occurrence of a better contractility in the more "damaged" segments should be very unlikely.

Moreover, the complete normalization at 6 months of the glucose uptake in the presence of a normal echocardiogram, enforces the correlation between the observed decrease in contractility and the reduced FDG uptake.

Hence, we may state that the reverse mismatch in our patient reflects a real reduction in F18-FDG myocardial uptake, expression of a reduced rate of exogenous glucose utilization. This necessarily leads to decreased glycolysis, because this metabolic pathway may be compared to a funnel, the efflux from which is principally controlled by the amount of glucose poured into it.

Since, with time, the initially akinetic segments recovered full contractility, they must have been viable during PET. A metabolic shift towards other substrates

must have necessarily occurred to produce the energy needed to maintain viability. Unfortunately, we were unable to evaluate the free fatty acid metabolism with C-11 palmitate and the oxidative metabolism with C-11 acetate.

But how could a reversible damage to the myocardium decrease its glucose metabolism? Some authors have suggested that in patients with chronic and acute coronary artery disease a reverse mismatch could be explained by the presence of a mixture of fibrous and viable myocardium[3]. This seems possible in patients with ischemic heart disease in whom functional recovery may or may not occur over time. But this was not the case in our patient because the coronary angiogram was completely normal and there was a complete normalization in contractility.

Some other hypotheses may be proposed. These are not exclusive of one another because they may be interpretative of the same phenomenon occurring at different levels.

Glucose uptake is mediated by the translocation of transporters from an intracellular storage pool to the sarcolemma. Glucose transporter (GLUT)-4 and GLUT-1 are the primary forms of the GLUT family expressed in the adult human myocardium[10]. While GLUT-1 is generally considered to be responsible for the basal glucose utilization, GLUT-4 is primarily regulated by insulin secretion and increases in case of a high workload and after a glucose load. It is possible that severe, but not irreversible, damage may limit the myocardial glucose uptake *in vivo* by decreasing the intracellular trafficking of GLUT-4. Another mechanism could depend on the direct inhibition of glycolysis by a decreased intracellular pH.

However, a more detailed biochemical explanation, in the search of a link between metabolism and function, would be more appealing. It is widely accepted that the so-called "proinflammatory" cytokines and nitric oxide (NO) are produced during a variety of situations of myocardial stress, including ischemia and infection. The cardiac depression observable in some situations may be mediated by the local production of cytokines such as interleukin-1β or tumor necrosis factor-α[11], through the induction of NO synthase and the production of NO, a free radical gas with a very short half-life. The action of NO is mediated by the second messenger cyclic guanosine monophosphate that, owing to the inhibition on glucose uptake that it exerts when its concentrations are elevated, also influences intracellular metabolism[12]. Thus, we hypothesize that NO overproduction in somehow injured myocardium can induce both mechanical effects by depressing contractility as well as a metabolic shift from the utilization of glucose to some other substrate. On the basis of information deriving both from echographic as well as nuclear studies, this could have been the case in our patient.

In conclusion, the *in vivo* evidence of reverse mismatch, accompanied by the recovery of myocardial mechanical function with time, clearly shows that viability is not always dependent on FDG uptake; rather a reduction in glucose metabolism in the presence of a normal perfusion may also prelude the normalization of a depressed contractility.

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