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SHORT COMMUNICATION

# Suppression of myocardial glucose metabolism in FDG PET/CT: impact of dose variation in heparin bolus pre-administration

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## Abstract

**Introduction** Adequate suppression of physiologic myocardial glucose uptake is important to ensure the interpretability and diagnostic reliability of [$^{18}$F]fluorodeoxyglucose (FDG) PET/CT studies performed in the context of cardiac inflammation and infection. This study describes our experience with 4 preparatory protocols used in our institution.

**Methods** FDG PET/CT scans were performed according to 4 preparatory protocols (716 scans total), i.e. 6-h fast (group 1), low-carbohydrate diet plus 12-h fast (group 2), low-carbohydrate diet plus 12-h fast plus intravenous heparin pre-administration (15 IU/kg) (group 3), and low-carbohydrate diet plus 12-h fast plus intravenous heparin pre-administration (50 IU/kg) (group 4). Consecutive scans were retrospectively included from time frames during which the particular protocol was used. FDG uptake in normal myocardium was scored on a scale ranging from 0 (uptake less than that in the left ventricular blood pool) to 4 (diffuse uptake greater than that in the liver). Complete suppression was defined as uptake less than or equal to the blood pool (scores 0–1).

**Results** Complete suppression was accomplished in 27% in group 1, 68% in group 2, 69% in group 3 and 81% in group 4. Complete suppression was significantly lower in group 1 compared with all other groups ($P < 0.0001$ for all comparisons) and significantly higher in group 4 compared with group 2 ($P = 0.005$) and group 3 ($P = 0.007$). Groups 2 and 3 did not differ significantly ($P = 0.92$).

**Conclusion** A total of 50 IU/kg single-dose heparin administration before FDG PET/CT in addition to a low-carbohydrate diet and prolonged fast significantly outperformed protocols with no or lower dose (15 IU/kg) heparin in completely suppressing myocardial glucose metabolism.

**Keywords** FDG PET/CT · Cardiac glucose metabolism · Low carbohydrate diet · Heparin · Infection · Inflammation

## Introduction

[$^{18}$F]Fluorodeoxyglucose (FDG) positron emission tomography with CT-based attenuation correction (PET/CT) is increasingly used for the detection of cardiac inflammation and infection [1].

This article is part of the Topical Collection on Infection and inflammation.

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As glucose metabolism, and therefore the uptake of FDG in the myocardium, shows a high physiological variation, it is important to optimize patient preparation to suppress the physiological glucose metabolism to reliably differentiate between physiological and pathological uptake of FDG. As described earlier [2], uptake in normal myocardium is dependent mainly on insulin, blood glucose levels, and blood free fatty acid (FFA) levels in accordance with the Randle cycle [3]. Type 4 cellular glucose transporter (GLUT4) mediates myocardial glucose metabolism, whereas GLUT1 and GLUT3 mediate the increased glucose consumption of inflammatory cell responses. By manipulating the GLUT4 response, it is possible to suppress myocardial glucose consumption independently of inflammatory processes, and there are many different protocols in use for this purpose [4].

The aim of this study was to retrospectively compare the efficacy of 4 methods of myocardial suppression used in our hospital, i.e. the standard 'oncologic' preparation (≥6-h fast,

group 1), a low-carbohydrate diet with a prolonged fast ≥ 12 h (group 2), and a low-carbohydrate diet with a prolonged fast ≥ 12 h and heparin pre-administration as a bolus of 15 IU/kg (group 3) or as a bolus of 50 IU/kg (group 4).

## Methods

### Patient selection

Prior to February 2017, the protocol for myocardial glucose uptake suppression in our hospital consisted of 24 h of low-carbohydrate fat-allowed diet including a fast of at least 12 h (LCD). Based on the ASNC guideline for cardiac SPECT/CT and PET/CT [5], an intravenous bolus of 15 IU/kg of heparin 15 min before the administration of FDG was added to the protocol in February 2017. After a clinical comparison of the effect of these two protocols, the dose was increased to 50 IU/kg in September 2017 up to the present day. We, thus, included and grouped patients accordingly: 6-h fast (oncology preparation, group 1), low carbohydrate diet plus 12-h fast (group 2), low-carbohydrate diet plus 12-h fast plus intravenous heparin pre-administration (15 IU/kg) (group 3), and low-carbohydrate diet plus 12-h fast plus intravenous heparin pre-administration (50 IU/kg) (group 4). All protocols included instructions to avoid exercise starting the day before scanning. Group 3 was the only group with a finite number of available patients of 187. We included 185 consecutive patients for each of the other groups.

Informed consent was waived by the local ethical committee based on the retrospective nature of the study.

Excluding dietary protocol violations, i.e. inadequate adherence to the diet and/or fasting time ($N = 23$), glucose levels > 10.0 mmol/L ($N = 1$), ischemia explaining focal FDG uptake ($N = 1$) and image quality too poor for evaluation due to motion artefact ($N = 1$), the number of scans available for analysis was 179 in group 1, 179 in group 2, 169 in group 3 and 189 in group 4 for a total number of 716 scans. Group characteristics are outlined in Table 1.

### Imaging

All scans were performed at the Meander Medical Center using one of two PET/CT systems (Biograph mCT; Siemens) approximately 60 min after administration of approximately 2 MBq/kg of [$^{18}$F]FDG with unenhanced CT images for attenuation correction using a 1.0 pitch, a 10-mm slice thickness, 120 kV, and 40 mAs, and PET using 3-dimensional acquisition, a field of view of 216 mm, and a 2.5 min/bed position scan time. PET/CT data were reconstructed using iterative ordered subsets expectation maximization (Gaussian filter, 4 iterations, 21 subsets). No dedicated cardiac images were acquired in any of the scan protocols.

### Scoring

Scoring was performed according to a visual scale as published earlier [2]. Possible scores are shown in Fig. 1. Scans were scored by a nuclear medicine specialist with 11 years of experience in cardiac imaging (AMS) and a nuclear medicine technician (AMB or NLSZ). In case of disagreement, the final score used in the analysis was based on consensus. Scores of 0 and 1 signified complete myocardial suppression. Scores 2, 3 and 4 were indicative of incomplete suppression, with no included images read as pathology by the reading physician. Scores were dichotomized into complete and incomplete suppression for the final analysis.

### Statistics

Continuous variables were compared between groups using 1-way ANOVA with post hoc Bonferroni analysis. Categoric sex and visual score distribution was compared between groups using the Pearson $\chi^2$ test. $P$ values below 0.05 were considered statistically significant, except in the Bonferroni analysis, for which $P$ values below 0.0125 (0.05/4) were considered significant.

## Results

### Patient variables

There was no significant difference in sex distribution across the four groups ($P = 0.08$). Weight did not differ significantly between the four groups ($P = 0.6$). Age and serum glucose did show significant differences between the groups ($P < 0.01$ for both). Post hoc Bonferroni analysis showed that for age, the values were significantly lower in group 3 (57.7, SD 16.2) compared with the other groups (group 1, 64.3; SD, 13.0; group 2, 62.8; SD, 15.6; group 4, 62.3; SD, 15.0; $P < 0.0125$ for all comparisons). For serum glucose, the values in groups 3 and 4 (5.1 mmol/L, SD 1.0, for both groups) were significantly lower than in groups 1 (5.7 mmol/L, SD 1.1) and 2 (5.4 mmol/L, SD 1.2) for nearly all comparisons; the difference between groups 2 and 3 did not reach the preset threshold for significance ($P = 0.014$, all other comparisons $P < 0.0125$). Values are shown in Table 1.

### Score distribution across groups

The distribution of scores per group is shown in Fig. 2. When comparing the score distribution between groups, group 1 differed significantly from all other groups ($P < 0.001$ for all

**Table 1** Group characteristics

| | Group 1 (malignancy) | | | Group 2 (inflammation/infection) | | | Group 3 (inflammation/infection) | | | Group 4 (inflammation/infection) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *N* | 179 | | | 179 | | | 169 | | | 189 | | |
| Male/female (%) | 84 (47%) / 95 (53%) | | | 79 (44%) / 100 (56%) | | | 94 (56%) / 75 (44%) | | | 102 (54%) / 87 (54%) | | |
| | Mean | *SD* | [range] | Mean | *SD* | [range] | Mean | *SD* | [range] | Mean | *SD* | [range] |
| Age (y) | 64,3 | *13,0* | [20-87] | 62,8 | *15,6* | [20-96] | 57,7 | *16,2* | [17-90] | 62,3 | *15,0* | [17-96] |
| Serum glucose (mmol/L) | 5,7 | *1,1* | [2.9-9.5] | 5,4 | *1,2* | [3.2-9.3] | 5,1 | *1,0* | [2.9-10.0] | 5,1 | *1,0* | [2.7-8.5] |
| Weight (kg) | 78,3 | *15,2* | [40-125] | 77,2 | *16,2* | [44-150] | 77,9 | *15,5* | [50-132] | 79,4 | *16,7* | [45-150] |

| Sex distribution between groups | $\chi^2$: 6.6606, p=0.08 |
|---|---|

| | | Age | Serum glucose | Weight |
|---|---|---|---|---|
| One-way ANOVA, P value | | 0,0003 | 0,00000002 | 0,60 |
| Post hoc Bonferroni, P values | 1 vs. 2 | 0,15 | 0,006 | 0,26 |
| | 1 vs. 3 | 0,00002 | 0,0000002 | 0,41 |
| | 1 vs. 4 | 0,08 | 0,000000003 | 0,25 |
| | 2 vs. 3 | 0,001 | 0,014 | 0,34 |
| | 2 vs. 4 | 0,37 | 0,002 | 0,10 |
| | 3 vs. 4 | 0,003 | 0,26 | 0,19 |

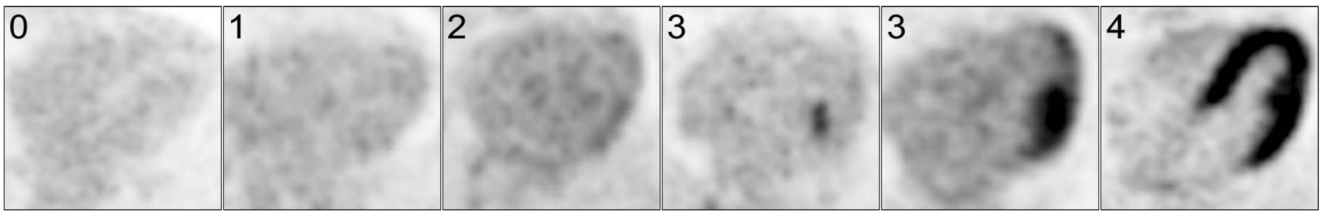
comparisons). Group 2 did not differ significantly from group 3 ($P = 0.95$). Group 4 differed significantly from group 2 ($P = 0.027$) but not group 3 ($P = 0.071$). After dichotomizing the data into complete and incomplete suppression, group 4 showed significantly higher complete suppression (81%) than both group 2 (69%, $P = 0.005$) and group 3 (68%, $P = 0.007$). Groups 2 and 3 showed no statistically significant difference ($P = 0.923$), and group 1 showed significantly less complete suppression than all other groups (27%, $P < 0.001$ for all comparisons).

## Discussion

Our data confirm that LCD significantly improves myocardial suppression over a 6-h fast without dietary restrictions, in line with earlier reports [2].

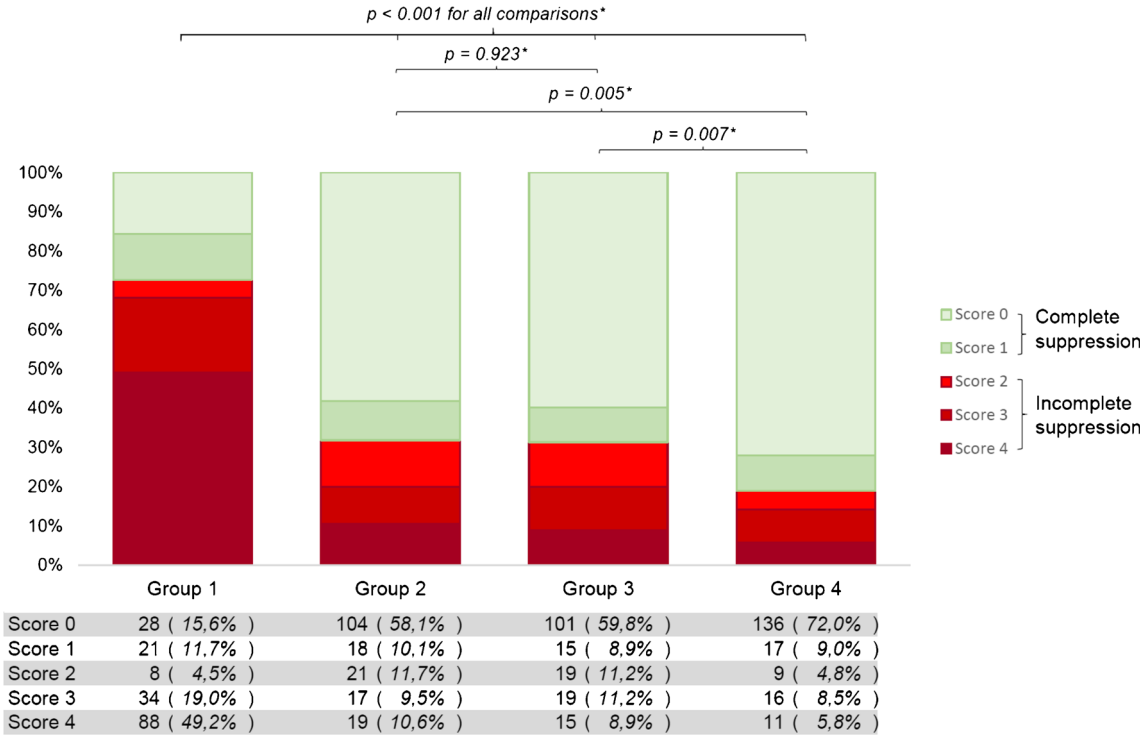
Based on the guidelines for cardiac SPECT/CT and PET/CT [5] and in vivo experiments in which a dose of 15 IU/kg of heparin elevated serum FFA levels but with little to no anticoagulant effect [6], it was assumed that this lower dose could improve myocardial suppression in a comparable manner with the higher dose of 50 IU/kg, which has been more extensively applied in protocols reported in the literature [2]. We did not find this effect in our cohort, as the level of suppression was not significantly different between groups 2 and 3. Conversely, we found an added effect for the higher dose of 50 IU/kg, improving suppression in roughly 1 in 10 patients. These results, while less pronounced, are in line with the earlier study comparing similar preparation protocols [2].

While other studies found less evidence for the additional value of heparin pre-administration [7, 8], our study compares the largest sample sizes to date and is only the second study to compare this dietary protocol with and without the addition of




| Score | Uptake criterion |
|---|---|
| 0 | Myocardium less than left ventricular blood pool |
| 1 | Myocardium equal to left ventricular blood pool |
| 2 | Myocardium greater than blood pool but less than liver |
| 3 | Myocardium focally greater than liver |
| 4 | Myocardium diffusely greater than liver |

**Fig. 1** Examples of scans and scores




| | Group 1 | Group 2 | Group 3 | Group 4 |
|---|---|---|---|---|
| Score 0 | 28 ( 15,6% ) | 104 ( 58,1% ) | 101 ( 59,8% ) | 136 ( 72,0% ) |
| Score 1 | 21 ( 11,7% ) | 18 ( 10,1% ) | 15 ( 8,9% ) | 17 ( 9,0% ) |
| Score 2 | 8 ( 4,5% ) | 21 ( 11,7% ) | 19 ( 11,2% ) | 9 ( 4,8% ) |
| Score 3 | 34 ( 19,0% ) | 17 ( 9,5% ) | 19 ( 11,2% ) | 16 ( 8,5% ) |
| Score 4 | 88 ( 49,2% ) | 19 ( 10,6% ) | 15 ( 8,9% ) | 11 ( 5,8% ) |

**Fig. 2** Score distribution per group. *Values based on dichotomized comparisons

heparin. To the best of our knowledge, it is the first study comparing heparin at doses of 15 IU/kg and 50 IU/kg. Additionally, we believe the added value depends on a synergistic effect in combination with LCD in our protocol as opposed to heparin alone or in less elaborate preparatory protocols. Additionally, a single bolus of 50 IU/kg may not be the only or the most effective way to add heparin administration to a preparatory protocol, as shown in a recent report incorporating three consecutive doses of 10 IU/kg into the protocol, but with a prolonged dietary period of 36 h [9].

The current Joint SNMMI-ASNC Expert Consensus Document on the Role of (18)F-FDG PET/CT in Cardiac Sarcoid Detection and Therapy Monitoring [10] considers heparin administration optional in the preparation for sarcoid FDG PET/CT imaging, tempered by the results of earlier studies [7, 8], and the recent Japanese Society of Nuclear Cardiology recommendations [11] do not recommend the administration of heparin before FDG PET/CT as a routine practice based on an assumed limited effect when compared with a fast of more than 18 h [8] and the risk of heparin-induced thrombocytopenia. In our study, no side effects of the heparin administration were reported. Although we believe longer fasting times to be one of the most, if not the most, important driving factors of our preparatory protocol, we are wary that even longer fasting periods might have a negative effect on patient adherence to the protocol. In our experience, a 12-h fast is generally well tolerated, but we have no experience with longer fasting times. Additionally, even in patients fasting > 18 h, an added effect of heparin pre-administration has been reported [12].

The optimal protocol for the suppression of myocardial FDG uptake is not yet clear, given the multitude of reported and possible combinations. A prospective study with repeated scans based on possible protocols in healthy volunteers would be of great value, but also difficult to implement due to cost and radiation exposure.

## Limitations

The main limitation of our study is its retrospective nature, limiting the available data. Serum insulin and FFA levels would have been especially interesting for further analysis, but were not part of our normal clinical routine. All adherence to the preparatory protocols was self-reported by the patients at the time of their scan, and it is likely that some breaches of protocol were not reported. However, as the dietary preparation was equal for all groups except group 1, we assume that inadherence to the protocol is equally distributed across the other groups. As the administration of heparin was performed under controlled conditions at our hospital, this step was not subject to patient reporting.

Although the 4 groups showed statistically significant differences in age and serum glucose values, the differences found were small in absolute terms with wide ranges of values. We doubt that the statistical significance of these differences translates to clinically significant effects on myocardial glucose metabolism suppression and the efficacy of the patient preparation protocols.

## Conclusions

A total of 50 IU/kg single-dose heparin administration before FDG PET/CT in addition to a low-carbohydrate diet and prolonged fast significantly outperformed protocols with no or lower single-dose (15 IU/kg) heparin in completely suppressing myocardial glucose metabolism.

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