Original Article
Variability in myocardial metabolism on serial tumor ^{18}F-FDG PET/CT scans

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Abstract: ^{18}F Fluorodeoxyglucose (FDG) positron emission tomography (PET) scans are performed routinely for oncologic patients. Myocardial uptake can vary among patients and between serial studies in the same patient. Our study aims to evaluate myocardial metabolism on staging FDG PET scans and to analyze factors influencing patterns of cardiac uptake, and their relevance. We analyzed retrospectively 100 PET-CT scans from 20 fasting lymphoma patients. Distribution of myocardial uptake was determined by visual assessment and the maximum standardized uptake value (SUVm) was calculated. Multiple variables were analyzed including: fasting length, cardiovascular risk factors, SUVm, and location of uptake. We found no correlation between fasting hours and cardiac uptake (*p*-value: 0.4786). There was a trend that showed less uptake in patients scanned in the afternoon versus the morning, although this was not statistically significant. The location of maximum uptake was unexpectedly variable in several patients and could not be ascertained to a specific cause. Interestingly, we found no correlation between cardiac risk factors and the amount of myocardial uptake. Myocardial FDG uptake is spatially and temporally heterogeneous. Differences in myocardial wall pattern and peak uptake exist and may not be explained by the length of fasting, gender, age or cardiac risk factors. This variability may occur in daily cardiac evaluations and affect interpretations of sarcoidosis and viability studies and should be further explored. A larger cohort study is necessary to confirm that our findings do not confer a higher cardiac risk profile to the cancer patient.

Keywords: Myocardial metabolism, cardiac FDG, fasting and FDG serial tumor PET, myocardial FDG heterogeneity

Introduction

The intricate mechanisms regulating myocardial metabolism in general and myocyte glycolysis specifically are quite complex and are dependent on a variety of factors including diet, fasting state, coexisting medical conditions (cardiac and non cardiac), coexisting medication effects on enzymatic processes, humoral and biological factors. Generally in the absence of circulating insulin, myocardial glucose uptake is limited and fatty acids represent the preferential source of energetics in an aerobic state. During conditions of reduced oxygen supply, the oxidation of all substrates cited above is decreased while anaerobic mostly glucose metabolism is activated [1, 2].

The introduction of 2-[fluorine-18] fluoro-2-deoxy-d-glucose (FDG) positron emission tomography (PET) has made it possible to study regional myocardial perfusion and metabolism in humans noninvasively. Camici et al. suggested that functional imaging may be valuable to study in vivo fatty acid and glucose myocardial metabolism changes in ischemic patients [2]. Additionally, Nakano et al. reported that a change in the preferential myocardial energy source from fatty acids to glucose may therefore be predictive of worsening coronary/ischemic heart disease [3]. These reports, which are discussed further, and the routine use of FDG PET/CT scans for staging and restaging of oncologic patients prompted us to study this phenomenon more.

It is not uncommon for the same patient to have multiple imaging studies. Myocardial uptake can vary among these patients and between serial studies in the same patient. The underlying reasons for this variability have not been explored. Current reports have discussed inci-

Table 1. Intrapatient variability in terms of change in pattern of myocardial uptake and change in wall distribution

Patient	Age	Sex	Cardiac Risk Factors	Change in wall pattern*	Change in location of peak uptake**
1	57	M	HTN, DM	No	No
2	64	M	Quit smoking 40 years ago	Yes	No
3	41	M	none known	Yes	Yes
4	33	M	none known	Yes	No
5	50	F	none known	Yes	No
6	21	M	none known	Yes	No
7	73	M	CABG, HTN, HL	No	No
8	12	M	none known	No	No
9	58	F	HTN, DM, HL	Yes	Yes
10	69	F	HTN, HL	Yes	No
11	25	F	none known	Yes	No
12	64	M	DM, HTN	Yes	No
13	29	M	none known	Yes	No
14	26	M	none known	Yes	No
15	64	M	none known	Yes	No
16	34	F	none known	Yes	No
17	35	F	HTN	No	No
18	44	M	none known	No	No
19	42	M	DM	Yes	No
20	58	M	none known	No	No

DM = Diabetes Mellitus, HL = hyperlipidemia, HTN = hypertension. *Change in wall pattern-refers to presence or absence of an observed change in the pattern of uptake during the 5 serial PET/CT scans, i.e. whether or not there is consistent pattern of uptake in any or none of the 4 myocardial walls. **Change in location in peak uptake-refers to presence or absence of an observed change in the location (anterior, inferior, lateral, or septal walls) containing the maximum FDG uptake (SUVm).

dental cardiac findings on tumor FDG PET scans in a fashion that is unrelated to the underlying myocardial metabolism [5-7]. We therefore wanted to explore whether myocardial glucose variability measured incidentally on routine oncology FDG PET scans was real and determine any factors driving this variability including but not only increased cardiac risk. In lieu of the above mentioned correlation of changes in glycolysis seen in patients with at risk myocardium. We therefore postulated that we might be able to detect higher risk cardiac patients incidentally on an oncology PET, by detecting variability or increases in myocardial metabolism in this cohort. We also hypothesized that cardiac uptake may have a direct relationship with the fasting period per scan.

Materials and methods

Our study's aim was to evaluate myocardial metabolism on serial staging tumor FDG PET scans and to analyze deterministic factors influencing patterns or distribution of cardiac uptake, and their relevance. The study was approved by the Institutional Review Board of Yale University School of Medicine/Yale New Haven Hospital. We performed a retrospective review of 100 PET-CT scans from a total of 20 men and women with a history of lymphoma. These lymphoma patients had undergone at least 5 serial FDG PET-CT scans each. All PET-CT studies were performed on a General Electric (GE) Discovery ST PET-CT. The two scanners (GE Discovery DST-E and the GE Discovery D690 PET/CT) both have similar LYSO crystals and reconstruction protocols. The imaging protocol is standard oncologic PET protocol with administered FDG doses of approximately 15 mCi (555 MBq) with an approximately 60 minute post-injection delay.

The number of fasting hours was obtained from a standard questionnaire provided to each patient prior to the examination. We also recorded the time of the scan (morning versus afternoon), to determine whether or not the time of the PET/CT had an effect on myocardial metabolism. The distribution of myocardial uptake within the regional left ventricular wall was also determined by visual assessment. Additionally, the maximum standardized uptake value (SUVm) was calculated using a GE Advantage Workstation (GE Healthcare) and this value was localized to the relative position (basal, mid and apical) in each of the four walls of the left ventricle (anterior, lateral, inferior, septal).

The relationship between myocardial uptake and fasting was determined using linear regres-
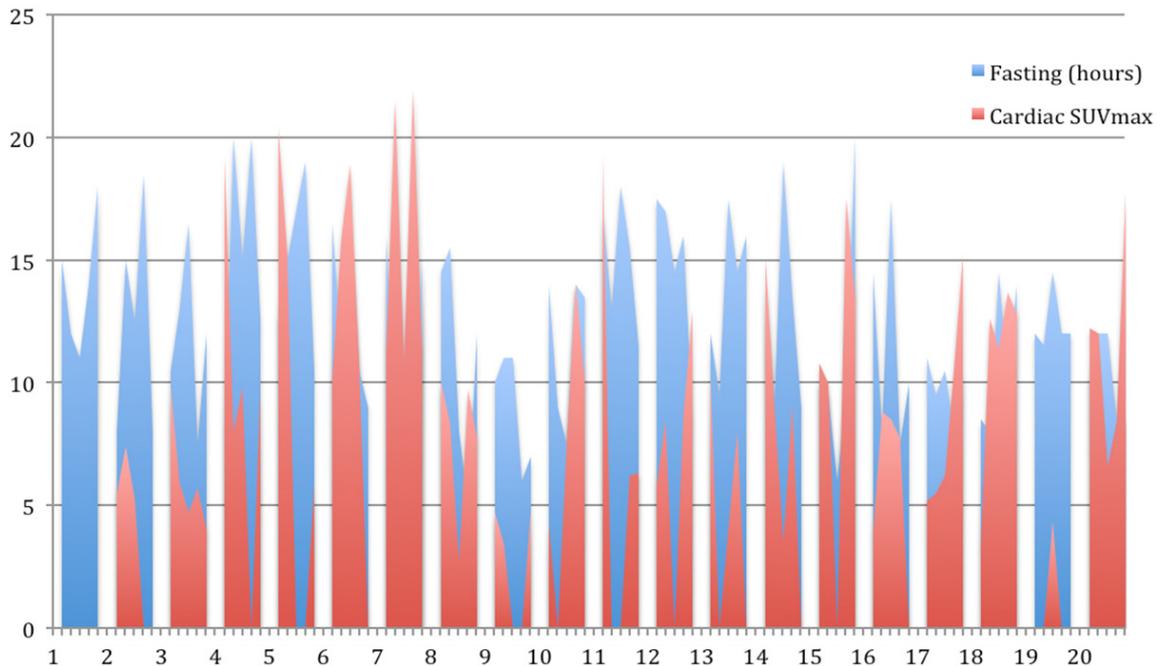
Figure 1. Relationship of length of fasting and maximum standardized uptake value (SUVm). Plots of 'fasting length' and 'SUVm' show a very different pattern, which supports that the length of fasting does not significantly alter the uptake (SUVm). The x axis represents every patient from 1 to 20. The y axis represents hours (blue) and semi-quantitative SUVm (red). Patient 1 has no uptake (SUVm=0) with a lengthy fasting period > 12 h on all 5 scans in contrast with other patients with lengthy fasting periods and higher SUVm values.

sions. A categorical variable was created by dichotomizing those patients who had fasted for less than 12 hours and those that had fasted for at least 12 hours. The fasting variable was then regressed onto the myocardial uptake variable. The relationship between SUVm and the length of fasting was found by taking the raw fasting variable (not dichotomized) and regressing it onto the SUVm variable.

Results

Of the 20 patients with a history of lymphoma in our retrospective study, 13 were male and 7 were female. The mean age was 45 years old (ranging from 12-73 years old). All patients had reported fasting for more than 5 hours, with some fasting more than 20 hours for some scans. Most of our cohort had no cardiac risk factors as shown in **Table 1**. No statistically significant correlation was found between the intensity of myocardial glucose metabolism as measured by cardiac SUVm and the length of fasting (*p*-value: 0.4786). We noted a trend towards less uptake in patients scanned in the afternoon versus the morning although this was not statistically significant.

When we looked at myocardial FDG uptake in different walls on serial scans, we found some variability in the presence or absence of uptake in similar walls between scans (**Table 1** and **Figure 1**). Additionally, we found that in a smaller number of patients, the walls involved with variable uptake patterns were different (**Table 1** and **Figure 2**). These findings were not related to the duration of fasting or cardiac risk factors (**Table 1**). Plots of 'fasting length' and 'SUVm' further (**Figure 1**) illustrates the lack of relationship between the length of fasting and quantitative cardiac uptake (SUVm). For example patient 1 has no uptake (SUVm=0) with a lengthy fasting period > 12 h on all 5 scans in contrast with other patients with lengthy fasting periods and higher SUVm values. The number of walls with uptake was recorded in every patient and on each of their five serial PET scans, and this was plotted to show no significant trend between the length of fasting and the regional wall distribution of FDG uptake (**Figure 2**).

Some of the patients demonstrate no appreciable pattern of uptake whatsoever on their
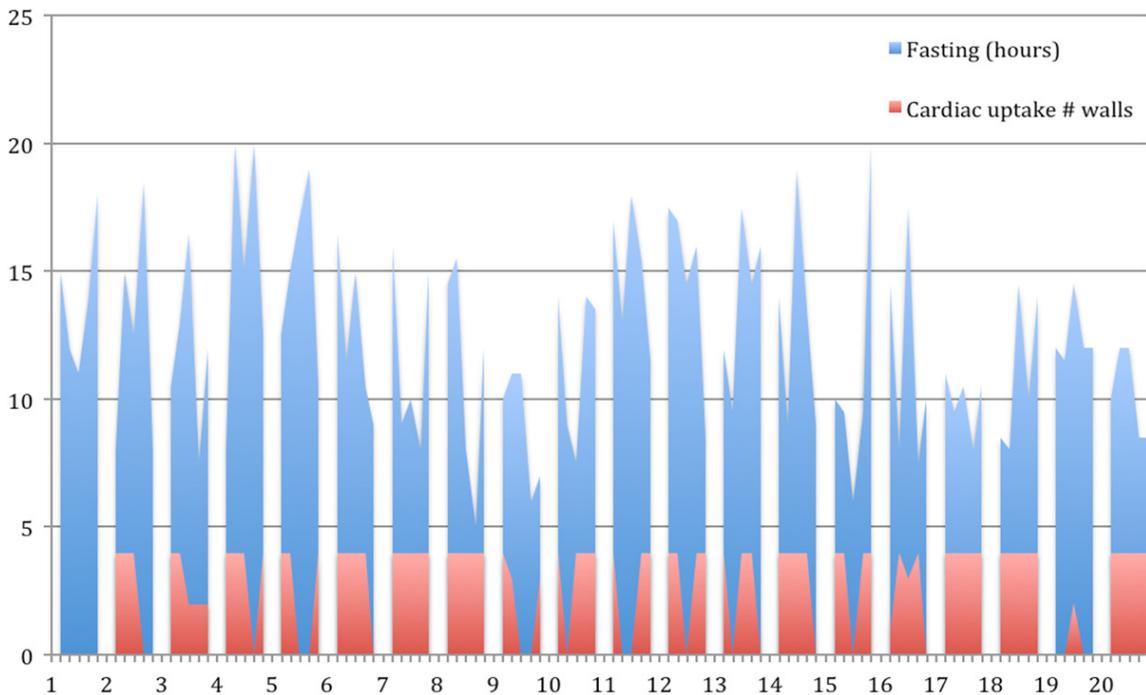
Figure 2. Relationship of length of fasting and regional wall distribution of FDG uptake. Plot showing no significant trend between the length of fasting and the regional wall distribution of FDG uptake. The x axis represents every patient from 1 to 20. The y axis represents length of fasting hours (blue) and the number of cardiac walls with uptake from 0 to 4 (red).
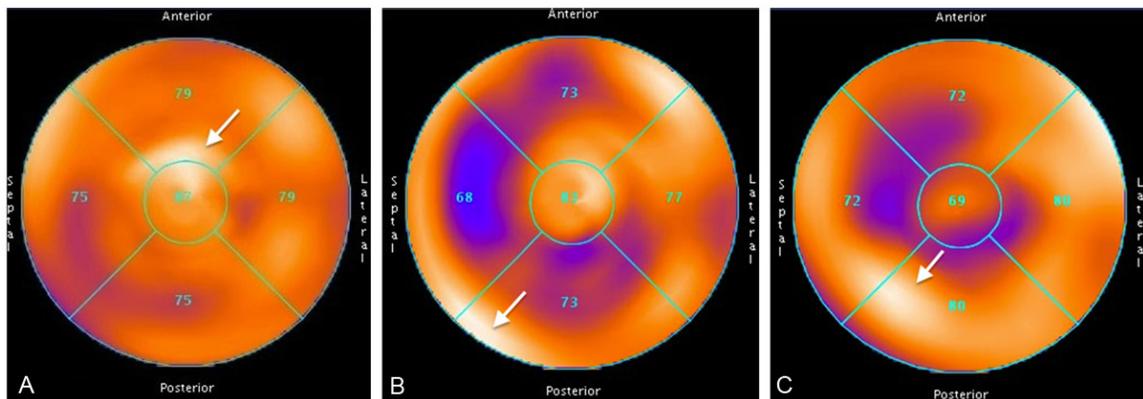

Figure 3. (A-C) Polar plots from three serial PET-CT scans in the same patient demonstrating variable uptake patterns, and different peak metabolisms (arrows). Fasting times for (A) was 8 hours, (B) was 15 hours, and (C) was 12.5 hours.

serial scans. For example, **Figure 3A-C** demonstrate polar plots for three serial scans of the same patient, which show different regions of maximum FDG uptake (SUVm) in the left ventricle, with each scan performed in the fasting state. Additionally, fourteen patients who fasted over 12 hours still had significant myocardial uptake, suggesting that the length of fasting alone may not be predictive of myocardial uptake alone. An example of one such patient who fasted over 14 hours is shown in **Figure 4**. Highly variable myocardial metabolism is depicted through the trajectories of each of the 20 patients' peak FDG uptake (SUVm), showing the marked inter-patient and intra-patient heterogeneity during the 5 serial PET scans,
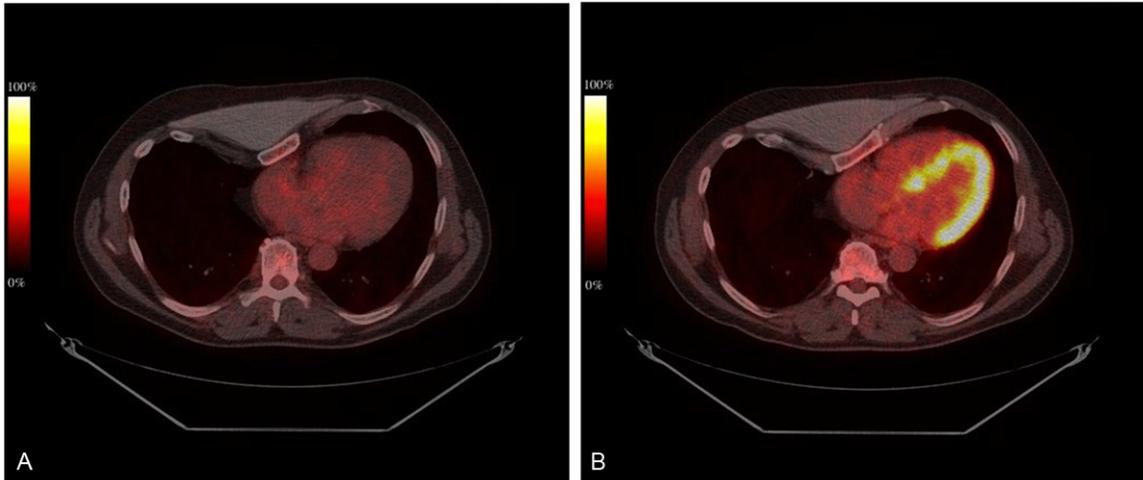
Figure 4. (A, B) Axial fused images from serial PET-CT scans demonstrating no cardiac uptake (A) versus uptake in all four walls (B) in the same patient who has fasted over 14 hours prior to both exams.
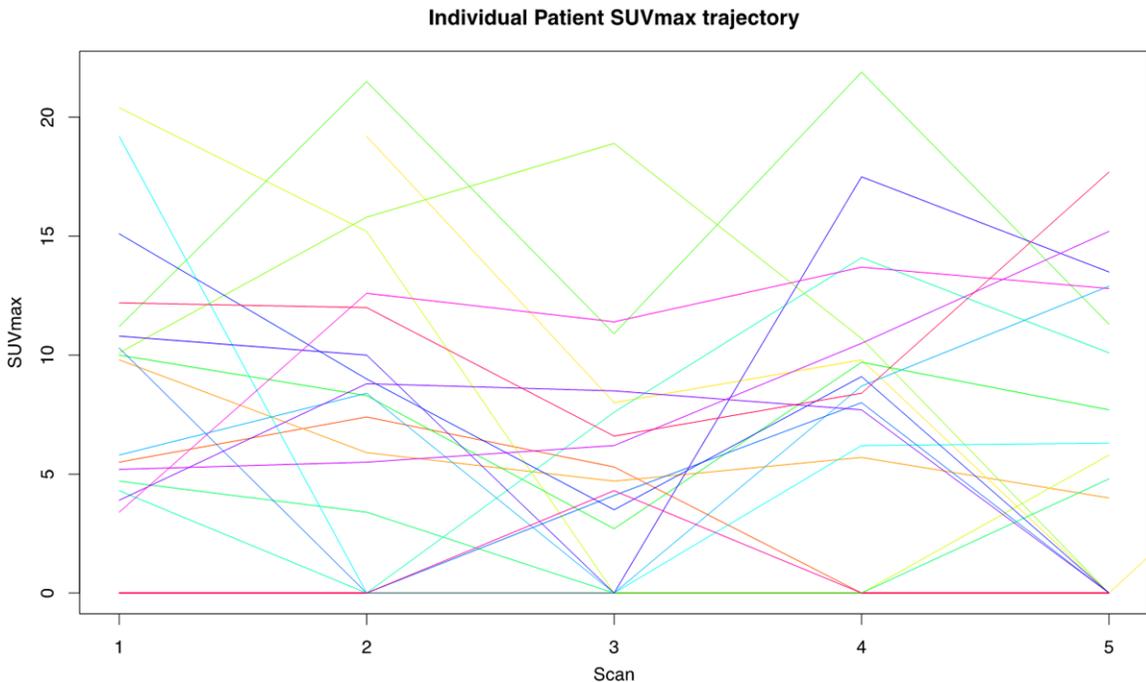
Figure 5. Graph showing variable peak myocardial uptake (SUVm) in 20 patients (each patient represented by a different color) during each of their 5 serial PET-CT scans.

despite all being done under fasting conditions (**Figure 5**).

Discussion

Early on, Camici et al. reported on two basically different patterns of myocardial glucose utilization observed in patients with coronary artery disease studied at rest using FDG. In patients with stable angina on a home exercise regimen but studied at rest, regional myocardial glucose utilization was homogeneously low and comparable with that of a group of normals. In contrast, in patients with unstable angina, myocardial glucose utilization at rest was increased, even in the absence of symptoms and ECG signs of acute ischemia [1]. Nakano et al. found in a series of 67 ACS patients a trend towards increased FDG uptake in remote normoperfused myocardial tissue, more common in

patients with subacute myocardial infarctions and unstable angina as well as lower free fatty acid blood levels [3]. Araujo et al. had reported similar findings in the late 1980's [4].

On serial oncologic FDG PET/CT scans, the distribution of myocardial uptake can vary among patients and between individual studies. It has been reported that myocardial activity can interfere with the evaluation of the mediastinum, particularly when staging bronchial carcinomas [5]. The widely accepted protocol for these examinations is to perform the scans under fasting conditions. The Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM) practice guidelines recommend that FDG PET scans should be acquired after the patient has fasted for at least 4-6 hours [8]. In this fasting state, the amount of circulating glucose will be minimal, which will result in low levels of serum insulin and therefore less non-tumor (non target) uptake. FDG uptake by tumors will be enhanced in the fasting state, whereas cardiac uptake will be minimized [9]. Since many patients are asked to be 'NPO' after midnight on the day of their PET scan, those scheduled later on in the morning or early afternoon may have prolonged fasting times for much longer than the minimum requirement. Occasionally, patients may fast for as long as 12 hours or more. It is unclear what the effect of these extended fasting periods truly is on myocardial glucose metabolism.

In our study, we show that the amount of regional myocardial FDG uptake is highly variable and is not significantly affected by fasting over five hours, which has been supported by other studies [11-14]. Since at our institution, our protocol restricts patients from eating or drinking within 4-6 hours, we do not have data from patients who fasted less than five hours. Nevertheless, our results show that the length of fasting alone cannot explain the variable myocardial metabolism. We also showed that our oncologic patients could have uptake in different regions during their serial PET scans. Hence the region of myocardium with high glucose metabolism can be variable in the same patient on different scans.

Additionally the intensity of myocardial glucose metabolism measured by maximal uptake (or SUVm) was found to change to different regions within the left ventricle in the same patient,

with no discernable pattern. This is contradictory to some studies that suggest a predominance of uptake in the lateral and posterior walls versus the anterior wall and septum [15, 16]. Other studies suggest that there is more likely to be uptake in the base of the heart than apically [6]. Still, no explanation for these reported patterns has been provided and our data does not support this.

Other than spatial heterogeneity, there has been reported to be a large variability in temporal distribution of FDG uptake throughout the myocardium as well [15, 17]. Similarly, we found that the same patient during five serial PET scans had no statistical reproducibility of myocardial uptake, independent of fasting times before each scan. Understanding this variability may have relevance in the interpretation of viability and sarcoid studies in cases where the preparation may affect positively or negatively the interpretation of the scan. It is unclear whether this variability is more common in the cancer patient.

Since fasting alone cannot explain the variability of myocardial metabolism, the influence on this complex physiological process is likely multifactorial. This variability may be in part due to levels of substrates such as glucose and free fatty acids, levels of hormones such as insulin, glucagon, epinephrine, dopamine and thyroxine, as well as other physiological and cellular processes such as myocardial blood flow and oxygen. Unfortunately, our study found that despite the patient's presence or absence of cardiac risk factors, there was no significant alteration of myocardial metabolism. This would have been a good biomarker to stratify cancer patients at increased risk for a future cardiac event. Our results are somewhat contrary to findings in another study, in which aging, left ventricular hypertrophy (LVH), dilated cardiomyopathy, diabetes mellitus, and obesity-related insulin resistance cause alterations in substrate metabolism of either glucose or fatty acids [18]. In these specific scenarios, Herrero et al. determined that the measurable shifts of metabolism can be used to understand the pathophysiology of cardiac disease, and may serve as potential therapeutic targets [18]. Hypertensive patients, who have an increased cardiac workload, may have a metabolic shift favoring glucose oxidation over fatty acids [19]. Interestingly, coronary artery disease (CAD) has been reported to cause left ventricular uptake in oncologic patients in the

fasted state [20]. Moreover, in the ischemic myocardium, glycolysis is stimulated and fatty acid oxidation is suppressed [10].

Our study showed no significant difference in myocardial metabolism between men and women in contrast with Israel et. al who found that men had significantly higher myocardial FDG uptake than women [21]. Another contradictory finding in this study was that the authors demonstrated that patients under 30 years of age had higher cardiac FDG uptake, whereas no significant correlation was found in our study and the cardiac risk of patient younger than 30 is inherently low. Arguments in support of gender and age-related differences in myocardial metabolism may attribute these to differences in cardiac cellular and molecular physiology. For example, in older patients there may be a decrease in GLUT4 levels, required for glucose transportation into the cell, as demonstrated in animal models [22]. Other possible factors for the variations in myocardial metabolism may include differences in diet, exercise, medications, and the severity of the particular disease of interest [14]. An assortment of drugs can affect normal myocardial distribution. The anti-hyperlipidemic drug, bezafibrate, and the synthetic thyroid hormone, levothyroxine, have been shown to lower myocardial FDG uptake [7]. On the contrary, benzodiazepines, such as diazepam (Valium), can increase cardiac uptake [21].

More importantly and what might relate to our study is that cancer therapies may have an impact on both spatial and temporal heterogeneity in oncologic patients. Radiation therapy may cause regional damage to the myocardium, thereby possibly causing altered uptake in these damaged areas [15]. Chemotherapy may have similar effects, either as a direct insult to the myocardium, through alterations in hormones, metabolites, and cytokines, or via direct stem cell effects. All of our patients had a history of Non Hodgkin's lymphoma. The choice of a single cancer diagnosis was meant to minimize the differential drug or diagnosis effect.

Limitations

The retrospective nature of our study limits our control of a variety of parameters that we may not be able to review/analyze as we are con-strained by documentation and clinical practice. We did not control for the content of our patients diet. It is unclear whether this would have affected our results. We did not correlate with myocardial perfusion study results or other cardiac imaging results, as these were not available in our cohort and may or may not have been performed in the allotted time of our study. Our cohort is also small even though we looked at 100 scans, as it is not trivial to find one patient with 5 serial scans.

Conclusions

Cardiac metabolism is a complex phenomenon. A variety of factors seem to affect the spatial and temporal heterogeneity of FDG uptake within the left ventricle. Regional myocardial wall differences in pattern and peak uptake of glucose can be seen and may not be explained by the length of fasting, gender, age or cardiac risk factors. The potential for this variability to occur in daily cardiac evaluations and affect interpretations of sarcoidosis and viability studies is real and should be further explored. Further exploration in a larger cohort is also necessary to confirm that our findings do not confer a higher cardiac risk profile to the cancer patient.

Disclosure of conflict of interest

None.

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