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FDG-PET Imaging of Doxorubicin-Induced Cardiotoxicity: a New Window on an Old Problem

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Abstract

Purpose of Review The present review focus on the published literature about the use of 18F-fluorodeoxyglucose (FDG) PET/CT imaging in the early recognition of anthracyclines-related cardiotoxicity.

Recent Findings The application of PET/CT may represent an early predictor of subsequent cardiotoxicity in cancer patients treated with doxorubicin (DXR). However, the application of PET/CT may also extend beyond mere cardiotoxicity identification and monitoring to provide mechanistic delineation of the cardiotoxic pathophysiology. Indeed, this tool further enriched the current knowledge on energy metabolism impairment in the DXR-induced cardiotoxic cascade.

Summary The capability of FDG to selectively track the early endoplasmic reticulum pentose phosphate pathway (PPP) response to oxidative stress rather than the later occurring contractile dysfunction might imply the abrupt occurrence of metabolic abnormality during the course of chemotherapy, possibly identifying the ongoing myocardial damage in time to change the chemotherapy scheme or to initiate targeted cardioprotective treatments. Future prospective studies encompassing a specific dietary or pharmacologic preparation before FDG injection, as already performed in infectious and inflammatory heart diseases, are needed to move the obtained preclinical findings supporting the role of FDG imaging in DXR cardiotoxicity from bench to bedside.

Keywords Cardiotoxicity · Fluorodeoxyglucose · Positron emission tomography · Doxorubicin · Oxidative stress

Introduction

Treatment effectiveness for solid and hematological malignancies significantly improved over the past four decades. In patients with Hodgkin lymphoma (HL), the 5-year relative survival rate increased from 72% in the years 1975–1977 to > 88% in the years 2003–2009 [1, 2]. Similarly, the 5-year survival rate increased from 57 to 69% in the same time interval for all cases of non-Hodgkin lymphoma (NHL) [1, 2]. This benefit, however, is partly counterbalanced by several adverse

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effects whose relevance is particularly evident after chemotherapy with anthracyclines whose administration is followed by an increased incidence of secondary neoplasms as well as an earlier appearance of degenerative cardiovascular disorders. These life-threatening side effects are further aggravated by a profound impairment in quality of life due to a series of conditions including cognitive impairment and reproductive deficiency, configuring young subjects as the population at higher risk for chemotherapy-related morbidity and mortality.

The incidence of these deleterious consequences increases with elapsing time for months and years after treatment completion. In fact, in patients with cancer diagnosis in childhood or younghood, chemotherapy-related morbidity and death rate become evident at the age of 40 years and further increase until the age of 50 years, when the cumulative incidence of a self-reported severe, disabling, or fatal condition reaches values 2.5-fold higher than those of sibling controls (53.6% vs 19.8%) (http://www.cancer.gov/types/childhood-cancers/late-effects-hp-pdq#section/_4).

A vast literature indicates that oxidative stress and its ubiquitous distribution at least partially justifies most of the systemic toxicity induced by anthracyclines (e.g., doxorubicin, DXR). This notion has been intensively studied for the heart in which DXR has been found to damage nuclear DNA, mitochondrial function, protein synthesis, and intracellular calcium homeostasis through several ROS-dependent pathways able to irreversibly accelerate senescence-like changes in cardiomyocytes [3]. In agreement with the clinical observation, most of these alterations persist and even progress after treatment discontinuation. Thus, therapeutic doses of DXR seem to enhance an irreversible damage able to induce a progressive impairment in contractile function up to the eventual development of a clinically overt heart failure. Despite this peculiar time evolution, the pathophysiological mechanisms underlying this sequence of events remain largely unknown, hampering the effectiveness of interventions to treat the development of cardiotoxic consequences of chemotherapy. A similar consideration also applies to the development of prevention strategies [4•], since most current diagnostic approaches focus on the consequences of the irreversible DXR-related damage (early or overt deterioration of left ventricular contractile function) but do not elucidate the preceding pathophysiological alterations in cardiomyocyte phenotype regulation [5]. As a consequence, clinical strategies are barely focused on chemotherapy-induced cardiotoxicity and most often tarte heart failure as its severe and late complication.

In this scenario, several studies have been published in the last few years showing the systematic occurrence of a peculiar metabolic response to chemotherapy. Indeed, DXR has been found to induce a significant increase in myocardial FDG accumulation that persists for years after treatment discontinuation. This observation opened a new window on the possible role of FDG-PET/CT as an early biomarker of myocardial damage for the modern cardio-oncological practice. As discussed below, this approach seems to explore the activation of a pathophysiological pathway directly involved in the development of cardiotoxicity while conventional strategies only interrogate its late consequences (echocardiography) or its very early phases (troponin assays). From a practical point of view, FDG-PET/CT offers the unique advantage of being routinely performed in a high percentage of cancer patients allowing cardiac evaluation without increasing healthcare costs or radiation burden. The present review focus on this perspective, extending the clinical observations to the preclinical interpretation of the role of energy metabolism in DXR-induced cardiotoxic cascade and its clinical consequences.

The Clinical Observation (the Bedside)

In cardiology, FDG imaging has been introduced for more than 30 years for the detection of residual viability in patients with left ventricular dysfunction and coronary artery disease [6]. This utilization aims to identify all those regions in which cardiomyocyte glucose metabolism and GLUT expression are preserved interrogating "maximal" FDG uptake under insulin-stimulated membrane docking of GLUT-4. To this purpose, tracer injection must be preceded by the administration of a glucose load. By contrast, oncological use of FDG imaging aims to verify "minimal," GLUT-1-dependent, tracer uptake. Tracer is injected under fasting condition resulting in a relatively low and often heterogeneous myocardial FDG uptake [7]. Therefore, changes in cardiac tracer retention can be considered as an index of a shift in metabolic pattern primarily affecting cardiomyocytes and scarcely dependent upon hormonal stimulation.

The potential role of FDG uptake as an index of cardiac toxicity was first suggested by Borde et al. [8] who reported an unexpected increase in myocardial FDG standardized uptake value (SUV) in post-therapy PET/CT scans compared with the baseline in 8/12 lymphoma patients. This response was associated with the administration of relatively higher DXR doses. This observation was interpreted as a possible index of a dose-dependent DXR effect on cardiac glucose metabolism.

Based on this observation, we retrospectively evaluated a group of HL patients successfully treated with the conventional Adriamycin (DXR), bleomycin, vinblastine, and dacarbazine scheme (ABVD) and submitted to a clinical follow-up to the acquisition of the control PET/CT 1 year after treatment discontinuation. In the whole group, cardiac FDG uptake progressively increased during therapy administration and remained elevated for at least 1 year [9••]. During this observation period, cardiac abnormalities developed in 31% of patients. In these subjects, pre-therapy myocardial SUV was markedly lower with respect to the remaining ones showing preserved contractile function at follow-up [9••]. However, in these same patients, cardiac SUV markedly increased until the end of therapy when it was inversely

correlated with the subsequent deterioration of contractile function at follow-up echocardiography, Fig. 1 [10]. Intriguingly, this metabolic activation was not explained by an increase in heart rate or aortic pressure at cardiologic examination, ruling out any significant contribution of shifts in LV energy expenditure caused by an increased workload. On the other hand, the long-lasting increase in cardiac FDG uptake after DXR discontinuation combined with its generalized occurrence in virtually all studied patients intrinsically implies a minor (if any) influence of the dietary regimen in the days immediately preceding the PET scan [7]. Rather, it identifies a direct, selective, and irreversible action of the drug on the left ventricular myocardium. In fact, the increase in cardiac FDG uptake persisted for at least 6 months after chemotherapy discontinuation, while skeletal muscle SUV showed a reversible response characterized by a significant increase during the treatment followed by a decrease back to baseline values in subsequent months.

This observation has been recently confirmed by Kim et al. [11••] who reviewed 121 consecutive breast cancer patients who underwent a complete monitoring protocol encompassing echocardiography and FDG-PET/CT images at baseline and after anthracyclines or trastuzumab administration. Again, a diffuse increase in FDG uptake was observed in the left ventricle after therapy in cancer patients. In addition, patients who subsequently developed clinically overt cardiotoxicity combined this response with a metabolic enhancement of the right ventricle FDG uptake that instead remained stable in the non-cardiotoxic group. The changes in both qualitative and quantitative parameters of myocardial FDG avidity were independent of age, previous radiotherapy, and chemotherapy regimen at logistic regression analysis. Actually, the agreement between right ventricular metabolic pattern and energy expenditure was not tested raising concerns about a possible role for an increased workload as a hydraulic consequence of the increased LV end-diastolic pressure caused by the contractile impairment. Nevertheless, the contractile impairment has been found to characterize both ventricles with a superimposable temporal trend and degree during trastuzumab therapy, suggesting a global and uniform effect of chemotherapy on myocardial metabolism [12].

From Bedside to Bench

The observations and the studies reported above suggest a potential role for FDG imaging, under fasting condition, in the stratification of risk for a cardiotoxic effect induced by anthracyclines therapy. However, this proof of concept studies cannot permit to consider this approach as a reliable tool in clinical practice. This application would indeed require prospective and controlled studies that, however, would ask for the selection of broad populations and very long follow-up observation times due to the relatively low incidence of clinically relevant cardiotoxicity and the great uncertainty in its timing. Such a huge effort would in turn be justified only in the presence of a reasonable hypothesis about the association between the early appearance of myocardial FDG signal and the later occurrence of contractile impairment. This task thus implies an accurate evaluation of basic and translational studies dealing with cardiac response to anthracyclines.

Since FDG uptake is almost universally considered a robust index of overall glucose consumption, first approaches to this issue obviously investigated whether DXR modifies glycolytic flux in different models of myocardial tissue. In cultured cells, Hrelia et al. reported that DXR 1 mM almost doubles the uptake of the FDG analogue 2-deoxyglucose in neonatal cultured rat ventricular cardiomyocytes in vitro [13]. This response matched the acknowledged capability of DXR to inhibit fatty acid oxidation and mitochondrial oxidative phosphorylation (OXPHOS) [14], triggering a Pasteur effect and thus increasing glucose consumption. This interpretation is further corroborated by the evidence that the acceleration in glycolysis flux is coherent with enhanced phosphorylation of adenosine monophosphate-

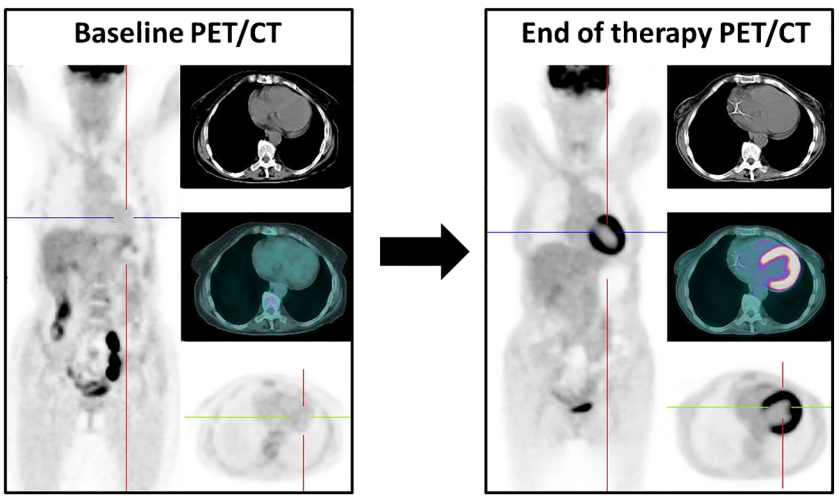

Fig. 1 Progressive myocardial increase of FDG uptake in a lymphoma patient treated with DXR. Example of baseline and post-therapy PET/CT scan of a 56-year-old female patient treated with ABVD scheme for HL showing an evident increase in myocardial metabolic activity following chemotherapy. At 12 months, the cardiological follow-up revealed the onset of moderate left ventricular dysfunction and pericardial effusion, without ischemic symptoms or signs

activated protein kinase (AMPK), the cell energetic sensor enhancing catabolic energy-producing pathways in response to a decrease in ATP/AMP ratio [15]. However, the direct relationship between this metabolic shift and energy depletion remains largely unclear, mostly because the increase in glucose consumption has been found to be transient and to rapidly disappear after drug removal [13].

To elucidate this issue, we performed dynamic analysis of FDG uptake in cultured heart myoblasts (H9c2) exposed to the same DXR concentration. Avidity for the fluorinated glucose analogue progressively increased in treated cultures with respect to the control ones [16••] (see also Fig. 2). This observation thus confirmed the previously reported data by Hrelia et al. Nevertheless, this agreement was only apparent since metabolic DXR effect selectively increased FDG uptake without significantly altering glucose consumption in cultured cells [16••]. Based on this paradoxical disagreement, we speculated that the increased tracer retention might reflect the metabolic response to the oxidative damage induced by DXR. This hypothesis was confirmed since the FDG uptake kinetics was significantly enhanced by the co-incubation of H9c2 cells with the antioxidant compound N-acetylcysteine (NAC) that participates to the antioxidant response enhancing the intracellular glutathione (GSH)-dependent reductive reactions (Fig. 2).

These experimental data thus document a relatively loose link between FDG uptake and glucose consumption and suggest that tracer uptake might represent an indirect index of the intracellular antioxidant response. Although somewhat disconcerting, this notion is not entirely new. Indeed, previous studies by our group documented a pivotal role of ER in FDG retention due to the catalytic function of the enzyme hexose-6P-dehydrogenase (H6PD). This autosomal counterpart of G6P-dehydrogenase (G6PD) is able to dehydrogenate a large number of hexoses, including 2-deoxyglucose-6P [17] within the endoplasmic reticulum (ER). In the brain, the higher H6PD expression explained the higher FDG uptake despite

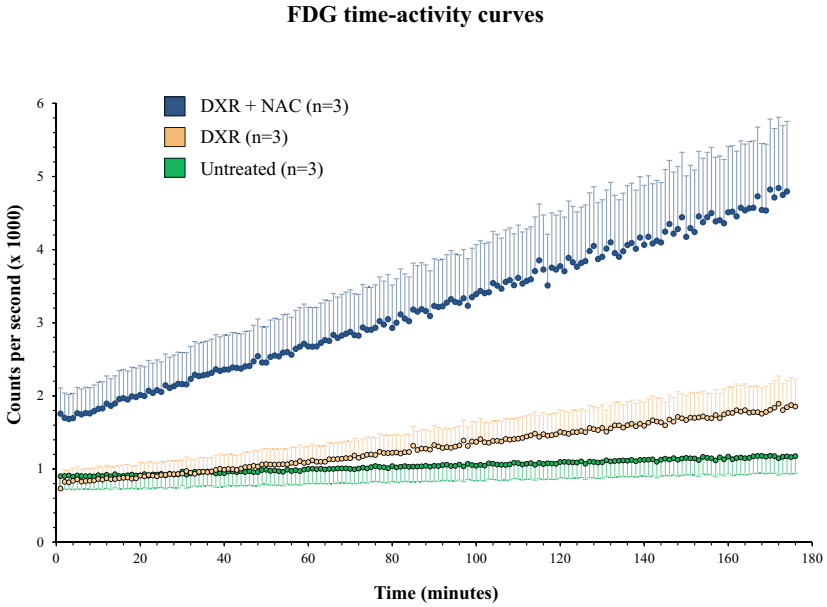

Fig. 2 FDG kinetics in H9c2 cultured cells exposed to DXR. FDG kinetics in H9C2 cultured cells was evaluated using a dedicated instrument: Ligand Tracer White (LT, Uppsala Se). LT harbors a 100-mm diameter Petri dish (PD) on a plate periodically rotating around an axis inclined at 30° from the vertical. An electron/positron detector faces the orbit zenith, while incubation medium is limited to its lowest part. Each cycle is divided into 4 intervals: (a) 25 s with cell culture in the rotation nadir and hence fully immersed in the radioactive medium; (b) 5 s for 180° rotation; (c) 25 s with cell culture in the zenith under the detector; (d) 5 s for 180° rotation and cycle restart. At each cycle (minute), the detector measures collected counts in phases (a) and (c) to estimate the counting rates (counts per second, CPS) of background and target cells, respectively. Time-activity curves were obtained by subtracting decay-corrected background counting rate from the corresponding target value through the whole 180-min experiment duration. The H9c2 cell line (American Type Culture Collection, Manassas, VA, USA) was grown at 37 °C in Dulbecco's modified Eagle's medium (DMEM; Gibco; Thermo Fisher Scientific, Inc., Waltham, MA, USA) containing 10% fetal bovine serum (Sigma Aldrich; Merck KGaA, Darmstadt, Germany) and 10% penicillin/streptomycin in an atmosphere containing 5% CO_2. A total of six experiments were performed for each culture condition. For each of them, a triplet of cultures was prepared: the first was used for cell counting, while the remaining two underwent radioactivity measurements. The phenotype of myocardial cells was verified under a light microscope (magnification, × 40). For all conditions, the culture medium was enriched with glucose at 11.1 mM concentration (2 g/L). At the time of the experiment, DMEM was removed from the PD and cells were covered with 3-mL solution containing glucose 5.5 mM (1 g/L) and FDG (2 MBq/mL, measured using a dose calibrator with an activity resolution < 10 kBq; Capintec CRC55) with or without DXR 1 μM. A third experimental condition was performed exposing H9c2 cells to DXR 1 μM and N-acetylcysteine (NAC) 50 μM. The figure displays average and SD values of time-activity curves (CPS, counts per second) measured in H9c2 cells by LT under control conditions (green, $n = 3$), DXR (orange, $n = 3$) or DXR + NAC 50 μM (blue, $n = 3$). H9c2 radioactivity progressively increased in all in vitro experiments confirming the expected accumulation kinetics of FDG. Adapted from Baucknehet al. [16••] with the addition of personal data

lower glucose consumption in neurons with respect to astrocytes [18, 19]. In colon and breast cancer, silencing H6PD expression almost halved FDG uptake despite a marked increase in glycolysis rate [20, 21]. Moreover, in cultured breast cancer cells, confocal microscopy showed that a significant co-localization of the FDG analogue 2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-amino]-2-deoxyglucose (2-NBDG) and ER membranes stained by glibenclamide. By contrast, this spatial agreement was profoundly impaired by silencing H6PD gene expression with interfering RNA siRNA [20]. Similarly, the role of the H6PD-driven ER machinery in intracellular FDG retention was further confirmed by mathematical modeling in cultured cancer cells [22].

In this scenario, the link between FDG accumulation and physiological response to redox stress might be explained by the H6PD catalytic function: this enzyme is able to trigger the first two reactions of reticular pentose phosphate pathway (PPP) that, in turn, is the main pathway to preserve the NADPH levels needed by GSH-mediated antioxidant defense mechanisms. In agreement with this concept, the decrease in FDG uptake caused by H6PD silencing was paralleled by a corresponding decrease in total NADPH content in breast and colon cancer models [20], subsequently confirmed by other labs that documented a preferential decrease of this coenzyme in the ER lumen [23••].

The role of NADPH in redox homeostasis in the cytosol is well established. In red blood cells, the absence of ER renders the conversion of this co-factor completely dependent upon the activity of the cytosolic enzyme G6PD. In patients with favism, G6PD deficiency hampers the NADPH-dependent regeneration of reduced GSH from the oxidized form (GSSG) rendering these patients susceptible to severe hemolytic crisis after the exposure to oxidative stress [24–26]. The selectivity of red blood cell response to these stressors confirms a relevant role for H6PD in all other ER-containing cells. Indeed, Rogoff et al. [27] previously demonstrated a profound dependence of skeletal muscle cells from H6PD since enzyme deficiency enhances the intracellular redox state and eventually results in a life-threatening myopathy.

Based on these observations, we tested the agreement between the persistently high cardiac FDG uptake, redox stress, and H6PD activity in the heart of mouse cancer models treated with therapeutic DXR doses (5 mg/kg). In these animals, myocardial FDG uptake remained abnormally high 1 week after drug discontinuation and was directly correlated with the degree of redox stress as depicted by the intensity of 2′,7′-dichlorofluorescein diacetate (H_2DCFDA) staining in myocardial slices prepared soon after micro-PET imaging [16••]. This effect was associated with increased H6PD activity in myocardial homogenates that strictly correlated with the corresponding FDG uptake [16••]. The hypothetical pathway underlying the link between FDG uptake and the H6PD-driven antioxidant response is summarized in Fig. 3.

In agreement with these data, Paik et al. [28] recently showed that endothelial cells exposed to hypoxia-induced oxidative stress conditions, ROS production plays a key role in triggering increased GLUT-1 expression, hexokinase activity, and, finally, FDG uptake. In this in vitro study, the NADPH oxidase-mediated ROS production was a major effector for the metabolic effect of hypoxia on endothelial cells since FDG uptake responses were completely blocked by the NADPH oxidase inhibitor, apocynin.

Similarly, in a canine model of radiotherapy-induced cardiotoxicity, which is largely related to ROS production, focal myocardial FDG uptake corresponding to the irradiated field was observed 3 months after radiation exposure [29]. At histological evaluation, all treated dogs displayed areas of myocardial damage in the irradiated field consisting of perivascular fibrosis and mild myocyte degeneration and mitochondrial injury, but interestingly, no inflammatory cell infiltration was detected, implying that FDG accumulation within the irradiated field directly involved cardiomyocytes and was not an index of inflammatory infiltrate [29]. Similar observations have been made in humans, in which the retrospective analysis of 39 lung cancer patients treated with radiotherapy showed that 47% of patients receiving 20 Gy to ≥ 5 cm^3 of the heart developed increased FDG uptake at PET imaging versus 0% of the patients who received 20 Gy to < 5 cm^3, again supporting the role of FDG as a marker of the ROS-mediated radiotherapy-induced myocardial injury [30].

Obviously, several other mechanisms might be involved in the increased FDG accumulation by the DXR-exposed myocardium. It has been suggested that this phenomenon might rely on a neuregulin (NRG)-mediated response [8]. NRG is a protein secreted by the endocardium and endothelium of cardiac vessels that might protect against DXR cardiotoxic damage enhancing glucose metabolism as an adaptive pattern [31]. On the other hand, Bulten and colleagues [32] recently identified a strong correlation between myocardial FDG uptake and HIF-1α expression in mouse models of DXR cardiotoxicity. HIF-1α is a hypoxia-driven transcription factor that regulates the expression of a variety of genes in response to a lack of oxygen which, in turn, is strictly involved in the activation of GLUT-1, GLUT-3, hexokinase, vascular endothelial growth factor, and several glycolytic enzymes [33]. However, the connection between these mechanisms and myocardial FDG accumulation has not yet been explored and further preclinical research in these fields are needed.

Conclusions and Future Perspectives (Back to Bedside)

Altogether, the present data suggest that the application of PET/CT may also extend beyond the mere cardiotoxicity identification and monitoring to provide mechanistic

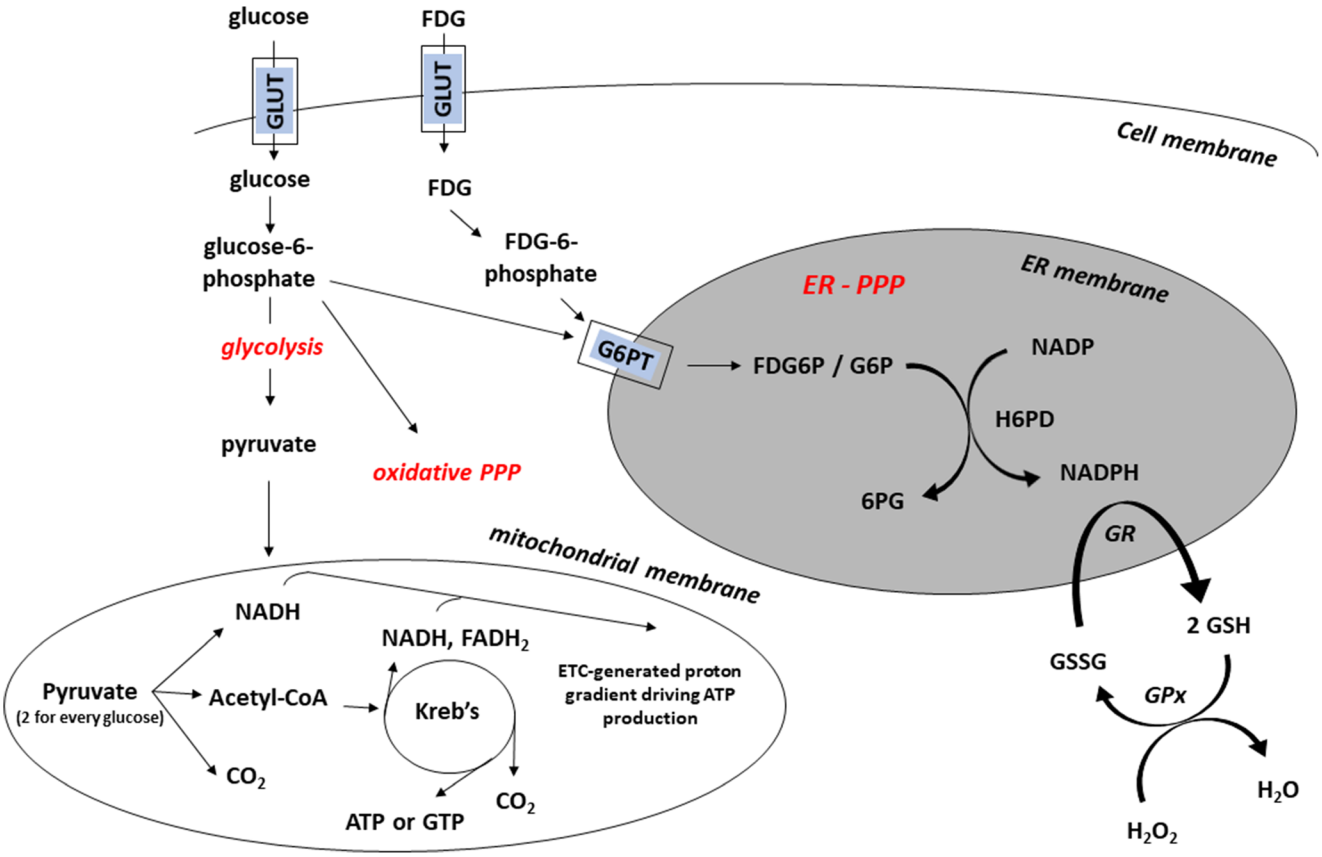

Fig. 3 Proposed pathophysiological interpretation of the link between DXR-induced oxidative stress and enhanced myocardial FDG uptake. The obligatory role of H6PD function in tracer uptake implies that FDG accumulation might be an index of H6PD activity rather than a surrogate index of glycolytic flux. This hypothesis might explain the strict correlation between the oxidative load (and therefore H6PD activity) and myocardial FDG accumulation after DXR exposure. PPP, pentose phosphate pathway; ER, endoplasmic reticulum; G6P, glucose-6-phosphate; G6PT, glucose-6-phosphate transporter; H6PD, hexose-6-phosphate dehydrogenase; GR, glutathione reductase; GSH, reduced glutathione; GSSG, oxidized glutathione; GPx, glutathione peroxidase

delineation of the cardiotoxic pathophysiology. In particular, whether confirmed in humans, the capability of FDG to selectively track the early ER-PPP response to oxidative stress rather than the later occurring contractile dysfunction might imply the abrupt occurrence of metabolic abnormality during the course of chemotherapy, possibly identifying the ongoing myocardial damage in time to change the chemotherapy scheme or to initiate targeted cardioprotective treatments. However, to move to clinical practice, the preclinical obtained result is not an easy task.

The major challenge is related to the inevitably unavailability of histopathological sections to be correlated with myocardial FDG uptake in patients undergoing FDG-PET/CT for oncological purposes. This intrinsic limitation hampers our capability to verify the correlation between FDG uptake and oxidative stress within the myocardium in humans. However, Todorova et al. suggested the feasibility of using the peripheral blood transcriptome as a potential surrogate biomarker of DXR-induced cardiotoxicity [34]. In their study, rat cardiac and peripheral blood mononuclear cells showed a superimposable gene expression profile after the administration of a single therapeutic dose of DXR. Most of the overexpressed genes fell into pathways related to oxidative stress response and protein ubiquitination. This finding opens a new window on the potential use of peripheral blood mononuclear cells as surrogate biomarkers of oxidative damage in patients undergoing FDG-PET/CT after chemotherapy to be correlated with myocardial FDG uptake.

From the clinical point of view, the considerable influence of dietary regimen in the days before FDG-PET/CT and the large variability of myocardial metabolic pattern under fasting conditions [7] ask for the development of precise guidelines to define a specific dietary regimen in patients studied for evaluation of chemotherapy effectiveness. This evaluation might be associated with heparin injection [35] duplicating the procedure currently performed to evaluate myocardial inflammatory condition such as endocarditis [36] or sarcoidosis [37]. On the other hand, standardized methods for images evaluation, potentially exportable to multicentral settings are needed to overcome the acknowledged limitations of SUV calculation, which might be influenced by several factors not related to tissue characteristics, including plasma glucose

concentration, length of uptake period, partial volume effects, and recovery coefficient, as well as FDG-PET/CT scanner sensitivity [38, 39].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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