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ORIGINAL ARTICLE

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In vivo measurement of myocardial oxidative metabolism and blood flow does not show changes in cancer patients undergoing doxorubicin therapy

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Abstract *Purpose*: The aim was to investigate in patients receiving doxorubicin whether any alteration in myocardial oxidative metabolism or blood flow as assessed by positron emission tomography (PET) could be observed either after the first dose of the drug, or during its chronic administration. *Methods*: Six female non-heart-failure cancer patients treated with doxorubicin were included in a longitudinal study. Resting radionuclide cineangiography and PET scanning with carbon-11 acetate were performed the day before the initiation of doxorubicin treatment at a dosage of 50 mg/m^2 every 3 weeks, and 3 weeks after the cumulative administration of 300 mg/m^2 (chronic toxicity). In addition, PET was performed 24 h after the first administration of doxorubicin (evaluation of acute toxicity). Myocardial oxidative metabolism and blood flow were assessed by PET (acute and chronic toxicity), and left ventricular ejection fraction was measured by radionuclide angiography (chronic toxicity). *Results*: Using PET for both acute and chronic toxicity evaluations, no significant effect of doxorubicin was observed either on the flux through the tricarboxylic acid (TCA) cycle or on myocardial blood flow. However, systolic left ventricular function showed a small but significant impairment after the administration of 300 mg/m^2 of doxorubicin. *Conclusions*: Other hypotheses should be explored to better explain the predominant mechanisms of the cardiotoxicity of anthracyclines in humans.

Key words Anthracyclines · Doxorubicin · Cardiotoxicity · Positron emission tomography

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Introduction

Cardiotoxicity has long been recognized as a complicating factor of cancer chemotherapy with anthracyclines such as doxorubicin (Adriamycin) [5, 21]. Systolic dysfunction as well as compliance and relaxation impairment can occur after either acute or chronic exposure to anthracyclines. Lee et al. [20] have reported that doxorubicin at a low cumulative dose (193 mg/m^2) impairs diastolic function (decreases left ventricular filling velocity). At higher cumulative doses (430–600 mg/m^2) doxorubicin decreases systolic function (as assessed by radionuclide angiography) in more than 60% of patients, whereas congestive heart failure occurs in 14% of patients [16].

Controversy exists regarding the mechanisms of cardiotoxicity of anthracyclines [9, 27]. Toxic endogenous substances (e.g. histamine, arachidonic acid metabolites, platelet-activating factor, calcium) may be released directly or indirectly by anthracyclines. Toxicity may also result from the generation of free radicals that can damage cell membranes. Based on histological data, it has been shown that the earliest ultrastructural changes involve swelling and disruption of mitochondria [33, 36]. This suggests the involvement of mitochondria in the cardiotoxicity of anthracyclines with the inhibition of ATP production and/or oxidative phosphorylation.

Consequently, the aim of this study was to investigate in patients receiving doxorubicin whether any alteration in myocardial oxidative metabolism and blood flow occurred either 24 h after the first administration of the drug, or during chronic administration of a cumulative

dose of 300 mg/m^2. Positron emission tomography (PET) was used to quantify both myocardial oxidative metabolism and blood flow, using carbon-11 acetate.

Patients and methods

Patients

Six female cancer patients aged 49–72 years participated in the study which was approved by the Claude Bernard University Ethical Committee in Lyon, France. Informed consent was obtained from all patients in the study. No patient had known cardiac disease, and all had a normal resting heart rate, blood pressure, electrocardiogram and left ventricular ejection fraction (LVEF) as assessed by radionuclide cineangiography (see below).

Study design

Cardiac evaluation consisted of clinical examination (including the measurement of the rate-pressure product, RPP), ECG recording, resting radionuclide cineangiography recording and PET scanning. This evaluation was performed on each patient at baseline the day before the initiation of doxorubicin treatment at a dosage of 50 mg/m^2 every 3 weeks, and 3 weeks after the last dose of doxorubicin after the cumulative administration of 300 mg/m^2 (chronic toxicity). In addition, PET was performed 24 h after the first administration of doxorubicin (acute toxicity).

Radionuclide technique

Radionuclide cineangiography was performed at rest. Ventricular function was assessed by equilibrium ECG-gated radionuclide ventriculography using technetium-99m in vivo-labeled red blood cells. Images were recorded in optimal left oblique anterior projection in order to avoid overlap between the right and the left ventricles. LVEF was measured from background-corrected end-diastolic and end-systolic counts after automatic selection of corresponding left ventricular and background regions of interest.

Positron emission tomography

Acquisition protocol

Scanning was performed using a time of flight seven-slice tomograph (TTV03, LETI, Grenoble) as previously described [23]. Emission scans were reconstructed in a 128×128 matrix using a Hanning filter with a cut-off frequency of 0.125 mm^{-1}. Transaxial resolution was 8 mm at the center of the field of view. After positioning of the patient, a 20–30-min transmission scan was performed, in order to achieve 15 million counts per slice. Patients lay in a supine position, and received a 20-s slow intravenous bolus of 10 to 15 mCi (7.4 MBq per kg) of ^{11}C-acetate [28] using an automatic pump. List mode acquisition was started simultaneously with the injection, and lasted for 30 min.

Image reconstruction and analysis

Seven "static" slices were reconstructed from 3 to 8 min to allow accurate positioning of regions of interest (ROI) on the myocardium. A dynamic series of 29 images for each slice had the following time sampling: 12×10 s, 4×30 s, 3×60 s, 7×120 s and 3×180 s images. This series was used to generate tracer kinetics in order to model myocardial oxidative metabolism and blood flow using an index of MVO_2 (k_{mono}) and an index of myocardial perfusion (IMBF) (see Myocardial perfusion and O_2 consumption modeling section). Image analysis was performed on SUN workstations using MEDIMAN [10]. Four to seven successive transaxial slices were selected in each patient for analysis. ROI were automatically defined on the static transaxial images using a sectorization procedure. Only remote and left anterior descending (LAD) regions were analyzed. Remote tissue time activity curves (TAC) were generated by averaging TAC from the posterolateral, posteroinferior or inferior walls, while LAD tissue TAC were generated by averaging TAC from anteroseptal, anterior, apical and apicolateral walls. Septal wall data were discarded to avoid right ventricle spill-over contamination. Data from anterobasal, lateral and apicoinferior walls were also discarded to eliminate ROIs with possible overlap between remote and LAD segments. In order to minimize spill-over from tissue to blood pool, the input function curve was generated with a 10-pixel diameter circle at the level of the mitral valve. Tissue TAC were corrected for spill-over and partial volume effect assuming an average myocardial wall thickness of 1 cm, as reported by Czernin et al. [11].

Myocardial O_2 consumption and perfusion modeling [17]

The k_{mono} approach of Armbrecht et al. [3] was used to quantify MVO_2, where k_{mono} was obtained after fitting TACs from 5 to 16 min. Estimation of myocardial blood flow was performed on the first 135-s kinetics using the two-compartment model approach described by Krivokapich et al. [19]. For each patient, k_{mono} and IMBF were displayed as the average of the data computed in the remote and LAD regions.

Statistical analysis

Data are expressed as the mean values and the corresponding standard errors. Variations in the RPP, IMBF and k_{mono} measurements were assessed using the Kruskal-Wallis one-way analysis of variance. The Wilcoxon signed rank test was used to compare the LVEF at baseline and after chronic administration of doxorubicin. The threshold of statistical significance was set at $\alpha = 5\%$.

Results

The main clinical characteristics of the patients are summarized in Table 1. One patient received doxorubicin alone (50 mg/m^2 every 3 weeks) and the remaining five patients received doxorubicin (50 mg/m^2 every 3 weeks) in association with cyclophosphamide and fluorouracil, both at a dosage of 500 mg/m^2 every 3 weeks. All the patients had a normal clinical cardiac evaluation and a normal ECG at rest.

The results (acute and chronic toxicity) are summarized in Table 2 which shows RPP, LVEF, and PET parameters (IMBF and k_{mono}). For acute toxicity, no significant effect of doxorubicin on the flux through the

Table 1 Baseline characteristics of the patients (*D* doxorubicin 50 mg/m^2 every 3 weeks, *F* fluorouracil 500 mg/m^2 every 3 weeks, *C* cyclophosphamide 500 mg/m^2 every 3 weeks)

Patient	Age (years)	Type of tumor	Chemotherapy
1	64	Digestive	D
2	64	Uterus	FDC
3	72	Breast	FDC
4	49	Breast	FDC
5	58	Breast	FDC
6	58	Breast	FDC

Table 2 Cardiac evaluation results displayed as individual data, and as mean and standard deviation (*IMBF* index of myocardial blood flow, *LVEF* left ventricular ejection fraction, *NA* data not available, *RPP* rate-pressure product)

Patient	Baseline				Acute toxicity			Chronic toxicity			
	RPP (mmHg · min^{-1})	LVEF (%)	IMBF (ml · g^{-1} · min^{-1})	k_{mono} (min^{-1})	RPP (mmHg · min^{-1})	IMBF (ml · g^{-1} · min^{-1})	k_{mono} (min^{-1})	RPP (mmHg · min^{-1})	LVEF (%)	IMBF (ml · g^{-1} · min^{-1})	k_{mono} (min^{-1})
1	6400	68	1.72	0.059	7300	2.13	0.072	7200	62	1.91	0.069
2	12000	55	1.93	0.089	13200	2.36	0.089	16500	35	2.03	0.085
3	11500	65	1.48	0.072	10400	1.99	0.084	8600	59	1.88	0.08
4	7500	61	1.52	0.067	8700	NA	0.078	8600	62	2.16	0.082
5	11600	62	2.18	0.083	9500	2.14	0.079	10500	51	1.9	0.078
6	12400	67	1.55	0.069	13000	1.57	0.069	13000	45	1.04	0.074
Mean	10233	63.0	1.73	0.073	10350	2.04	0.079	10733	52.3*	1.82	0.078
SD	2587	4.8	0.28	0.011	2362	0.13	0.007	3465	10.8	0.4	0.006

*$P < 0.05$ vs baseline

tricarboxylic acid (TCA) cycle was observed. However, there was a small but nonsignificant tendency for the IMBF to increase, but this result did not persist after its adjustment to the RPP. For chronic toxicity, no significant effects of doxorubicin were observed either on the myocardial oxidative metabolism or on IMBF. However, left ventricular systolic function as assessed by radionuclide angiography showed a small but significant impairment ($P = 0.046$) which was more pronounced in patients 2 and 6.

Discussion

Taking advantage of the unique properties of PET, we evaluated simultaneously myocardial oxidative metabolism and blood flow in cancer patients receiving doxorubicin therapy. As a functional imaging tool, PET offers the ability to explore noninvasively and to characterize directly human myocardial biologic processes that to date have been studied only in experimental animal systems. To our knowledge, despite the number of already published pharmacologic studies dealing with doxorubicin cardiotoxicity, such an approach has never been used in non-heart-failure patients receiving anthracyclines. The sample size of our study was small (six patients and 18 PET examinations) in relation to the sophistication and the high cost of the PET technique. However, the selected patient population was homogeneous and the aim of our study was mainly exploratory.

Carbon-11 acetate was chosen as the tracer because it has been demonstrated to provide indexes of both myocardial oxidative metabolism (flux through the TCA cycle) and myocardial blood flow [3, 17, 19]. The myocardium avidly extracts acetate, and in the cytosol the tracer is activated to acetyl-CoA, which is oxidized in the mitochondria by the TCA cycle to carbon-11 CO_2 and H_2O. In the case of close linkage to oxidative phosphorylation, the use of carbon-11 acetate allows the evaluation of myocardial oxygen consumption. More recently, myocardial perfusion has been estimated after carbon-11 acetate administration using a two-compartment model on its early 135-s myocardial kinetics. Such evaluations are performed with the analysis of the tissue activity clearance curves by exponential least-squares fitting routines, giving k_{mono} (i.e. estimation of myocardial oxidative metabolism) and IMBF (i.e. estimation of myocardial blood flow).

Baseline data

Before the first doxorubicin administration the data from our patients (k_{mono} and IMBF) were similar to those obtained at rest by Janier et al. [17] in normal subjects aged 23 to 27 years after adjustment to the RPP.

Acute Toxicity

This includes arrhythmias, ECG abnormalities, left ventricular dysfunction, pericarditis-myocarditis syndrome, and rarely myocardial infarction or sudden death [2, 6, 35]. The ECG changes are usually transient and occur in approximately 11% of patients (range 0 to 41%), whereas acute left ventricular dysfunction is a rare event which may occur in patients with marginal cardiac reserve. The earliest ultrastructural changes involve the sarcoplasmic reticulum and mitochondria. Such microscopic lesions have been reported to be present 14 h after a single dose of doxorubicin in mice [36]. Lesions progress in severity over 3–5 days culminating in vacuolar degeneration of the sarcoplasmic reticulum, swelling, disruption of the mitochondria and disorganization of the myofibrils. Similar lesions have been observed in humans. Endomyocardial biopsies 4 and 24 h after an initial dose of 30–60 mg/m^2 doxorubicin reveal swelling of the sarcoplasmic reticulum and mitochondria, with occasional nucleolar changes [33].

A single dose of an anthracycline rarely causes heart failure clinically, whereas acute exposure to anthracycline predictably causes severe dysfunction of isolated cardiac preparations. Ditchey et al. [13], for example, have noted that 20 min after intravenous injection of doxorubicin (1.5 mg/kg) into dogs, there is an acute impairment of cardiac output, left ventricular peak systolic pressure, and cardiac compliance and relaxation.

In our study, we did not observe any clinical sign of acute toxicity or find data suggesting major impairment of the flux through the TCA cycle 24 h after administration of 50 mg/m^2 doxorubicin. This does not mean that other mitochondrial functions were not modified after one dose of doxorubicin (see discussion on chronic toxicity). In addition, other mechanisms may mediate the acute toxicity such as the toxicity of endogenous substances or an autoimmune response [12, 26].

The nonsignificant tendency for an increase in IMBF 24 h after the first dose of doxorubicin may be related to an increase in cardiac output, perhaps in relation to patient stress (first administration of antineoplastic agents, adverse clinical effects of these agents, large number of laboratory examinations). When the IMBF was adjusted to the RPP, this tendency disappeared, so that no major increase in IMBF was identified in our study. Brown et al. [6] have shown that LVEF increases significantly 4 h after doxorubicin administration, which is consistent with the findings of Unverferth et al. [33] indicating an improvement in left ventricular function by echocardiographic dimensional changes and systolic time intervals at 4 and 24 h following treatment. Such an effect can be related to an increase in intracellular calcium or a release of catecholamines [9]. However, we cannot exclude the possibility that in our study small changes in loading conditions (RPP) following doxorubicin administration were responsible for the tendency of the IMBF to increase.

Chronic toxicity

In our study, radionuclide angiography showed a moderate but significant impairment of systolic function after the administration of 300 mg/m^2 doxorubicin. Like echocardiography, this technique has been shown to provide a sensitive and reproducible measurement of left ventricular dysfunction due to doxorubicin cardiotoxicity [1, 7, 14, 24, 29, 31, 32]. Sequential studies have demonstrated the frequent presence of subclinical left ventricular abnormalities, but the incidence of abnormal results may be increased if studies are performed after exercise. Left ventricular diastolic dysfunction occurs usually before systolic dysfunction so that both measurements are now recommended [8]. However, although no significant decrease in left ventricular systolic function is observed after moderate cumulative doses of doxorubicin, endomyocardial biopsies have shown drug-associated degenerative changes following doses greater than 240 mg/m^2. These changes consist of large vacuoles (corresponding to distended sarcoplasmic reticulum) which displace both contractile elements and mitochondria. Mitochondria exhibit positive calcium staining and electron-dense bodies (calcium inclusions?), suggesting an important role for mitochondria in the expression of anthracycline cardiotoxicity [26].

PET did not identify any important trend towards an impairment in IMBF or the flux through the TCA cycle after administration of 300 mg/m^2 doxorubicin. This may have been due to the relatively moderate cumulative dose of doxorubicin used. However, the absence of modification of oxidative metabolism may be explained by other mechanisms of cardiotoxicity of doxorubicin.

We cannot eliminate the possibility that doxorubicin inhibits the oxidative phosphorylation process [22] without any modification in the flux through the TCA cycle, as observed in our study. However, since blood flow in the myocardium is infrequently uncoupled from oxygen metabolism and blood flow is not changed, there is unlikely to be a change in oxidative phosphorylation. The fact that the TCA cycle turnover was not modified also strongly suggests that oxygen metabolism is not affected.

The free radical hypothesis has been thoroughly investigated [4, 15, 22, 30, 34], and is supported by the fact that anthracyclines increase lipid peroxidation. Such a hypothesis, already assessed in vitro, could be further investigated in patients using PET performed with carbon-11-labeled palmitate. Nevertheless, our study did not directly confirm any changes in oxidative phosphorylation which has intermittently been linked with the free radical hypothesis since the alterations at complex I of the electron transport chain (related to the generation of free radicals and to the formation of electrostatic complexes between doxorubicin and cardiolipin) are able to modify oxidative phosphorylation. In addition, other numerous limitations of the free radical hypothesis have already been pointed out [27]. For example, at cardiotoxic concentrations, anthracyclines fail to generate

free radicals or produce evidence of oxidative stress. Free radical scavengers also often fail to prevent doxorubicin cardiotoxicity [25].

Lastly, the calcium overload hypothesis (i.e. excessive levels of intracellular calcium leading to mitochondrial dysfunction) has been widely studied, but recent evidence suggests that calcium accumulation may be a result rather than a cause of anthracycline cardiomyopathy [18]. The predominant mechanism involved in in vivo anthracycline cardiotoxicity still remains to be determined.

Conclusion

After the administration of 50 mg/m^2 and 300 mg/m^2 (cumulative doses) doxorubicin to six cancer patients, and despite a small but significant decrease in left ventricular ejection fraction, PET using carbon-11-labeled acetate did not show any modification either of myocardial oxidative metabolism (i.e. flux through the TCA cycle) or of myocardial blood flow. Other hypotheses should be explored to improve our understanding of the mechanisms involved in the cardiotoxicity of anthracyclines in humans.

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