Myocardial Substrate Utilization and Left Ventricular Function in Adriamycin Cardiomyopathy

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We evaluated alterations of substrate utilization in a rat model of adriamycin cardiomyopathy with deteriorating left ventricular function. Rats were treated with adriamycin (2 mg/kg), once a week for 6, 8, 9 and 10 wk. Fluorine-18-F-deoxyglucose (^{18}F-FDG) and ^{125}I-beta-methyl-branched fatty acid (^{125}I-BMIPP) were used as tracers of glucose and fatty acid metabolism and ^{99m}Tc-hexakis (2-methoxyisobutyl-isonitrile) (^{99m}Tc-MIBI) was used as a myocardial blood flow tracer. Left ventricular ejection fraction (LVEF) calculated from gated blood pool images was used as an indicator of cardiac function. LVEF was normal in the 6-wk group (78.0% ± 4.8%), abruptly decreased in the 8-wk group (43.1% ± 10.1%) and further deteriorated in the 9-wk group (27.6% ± 13.4%). Accumulation of ^{18}F-FDG (%kgID/g) in the hearts of adriamycin treated animals progressively decreased compared to controls (2.19% ± 0.38%); 1.47% ± 0.42% ($p < 0.01$) at 6 wk, 1.22% ± 0.27% ($p < 0.001$) at 8 wk, 0.69% ± 0.56% ($p < 0.001$) at 9 wk and 0.50% ± 0.08% ($p < 0.001$) at 10 wk. This decrease occurred earlier than the deterioration in LVEF. Myocardial accumulation of ^{125}I-BMIPP decreased in the advanced stages of adriamycin cardiomyopathy and was well correlated with the decrease in ^{18}F-FDG accumulation. However, the decrease was less profound than for ^{18}F-FDG; 53.7% ± 9.8% versus 31.6% ± 25.4% of control at 9 wk (p = NS), 49.5% ± 15.3% versus 22.6% ± 3.5% of control at 10 wk ($p < 0.05$). Accumulation of ^{99m}Tc-MIBI did not differ between controls and the adriamycin treated groups. There were no differences in blood glucose levels between controls and adriamycin treatment groups. Both glucose and fatty acid utilization are decreased in adriamycin-induced cardiomyopathy and these critical impairments in energy metabolism are associated with heart failure. Impaired myocardial glucose utilization measured with ^{18}F-FDG may be a particularly sensitive marker of adriamycin cardiomyopathy.

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The myocardium can utilize a large number of substrates to provide the energy required for contraction. Under ordinary aerobic fasting circumstances, long chain fatty acids are the preferred fuel and glucose utilization is minimal. After carbohydrate loading, glucose is consumed to a greater degree. The relationship between regional oxygen delivery, as measured by myocardial perfusion, and glucose consumption has been used as an indicator of viable ischemic myocardium. In comparison to ischemia, congestive cardiomyopathy does not appear to produce a consistent change in substrate utilization that can be considered a hallmark of the process. Experimental studies have identified discordant results: fatty acid utilization has been shown to be decreased in cardiomyopathic hamster hearts (*1–6*), failing guinea-pig hearts (*7*) and in patients with congestive cardiomyopathy (*8*). Increased glucose utilization has been reported in cardiomyopathic Syrian hamsters (*9*) and in patients with congestive cardiomyopathy (*10*) or heart failure (*11*). In contrast, other reports have not detected an abnormality of glucose (*7,12–14*) or fatty acid utilization (*12–14*). Most of these studies have not correlated changes in metabolic substrate preference with ventricular function, to determine if alterations in substrate utilization precede deterioration of cardiac function.

Adriamycin cardiotoxicity is a dose-dependent process resulting in myocyte damage that culminates in congestive heart failure. Clinically evident congestive heart failure is a late manifestation of steadily accumulating subclinical myocardial damage. The mechanisms of toxicity are not clearly understood, but many studies suggest that adriamycin treatment results in free radical products and lipid peroxidation which disrupts myocardial cell membranes and associated enzymes (*15–17*). If the cytotoxic effects of adriamycin on myocyte membranes and membrane bound enzymes are important factors in subclinical myocardial damage, changes in myocardial metabolism may precede the observed changes in cardiac function and provide a useful clinical marker of cardiotoxicity.

In the present study, we evaluated the relationship between alterations in myocardial substrate utilization and left ventricular function in a rat model of adriamycin car-

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diomyopathy. Serial measurements of glucose utilization with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) fatty acid utilization with ^{125}I-beta-methyl-branched fatty acid (^{125}I-BMIPP) myocardial perfusion with ^{99m}Tc-hexakis(2-methoxyisobutyl-isonitrile) (^{99m}Tc-MIBI) and left ventricular ejection fraction (LVEF) with serial gated blood pool imaging were performed in rats treated with cardiotoxic doses of adriamycin.

MATERIALS AND METHODS

Materials

Adriamycin was supplied from Kyowa Hakko Kogyo Co., Ltd. (Tokyo, Japan). Aldrich Chemical Co. (St. Louis, MO) supplied 1,3,4,6 tetra-O-acetyl-2-O-trifluoromethanesulfonyl-beta-D-mannopyranose. Hexakis (2-methoxyisobutylisonitrile) (MIBI) was purchased from Dupont (Billerica, MA) and glucoheptonate kits were purchased from Squibb (Princeton, NJ). Iodine-127-labeled 15-(p-iodophenyl)-3-methylpentadecanoic acid and the nicotinyl hydrazine derivative of human polyclonal IgG were prepared by previously described procedures (*18,19*).

Radiopharmaceutical Preparation

Fluorine-18-fluorodeoxyglucose was prepared using a robotics-based implementation of the procedure developed by Hamascher et al. (*20*). Technetium-99m-IgG and ^{125}I-15-(p-iodophenyl)-3(R,S)-methylpentadecanoic acid were prepared by methods previously described (*18,19*). Technetium-99m-hexakis (2-methoxyisobutylisonitrile) was prepared according to the procedure of the manufacturer. Radiochemical purity was determined using ITLC-sg chromatographic strips (Gelman Laboratories, Ann Arbor, MI) or HPLC.

Animal Model

Male Wistar rats, weighting 250 ± 20 g, were treated with adriamycin (2 mg/kg s.c.), once a week for 6, 8, 9 and 10 wk (Fig. 1). Control rats were injected with saline. All animals had free access to a standard rat-chow and water up to the time of the study. At 2 wk after the final adriamycin treatment, metabolic and blood flow tracers were injected and gated blood pool imaging was performed.

Gated Blood Pool Imaging

The rats were anesthetized with ketamine and injected with 15 mCi of ^{99m}Tc-IgG. Fifteen minutes later, the animals were positioned supine and imaged approximately 1 cm from the 3-mm pinhole collimator of a large field of view gamma camera interfaced to a dedicated computer (Technicare model 438/Technicare model 560, Solon, OH). This configuration resulted in visualization of only the chest of the rat (approximately 12× magnification). Thirty-two gated images were acquired in the frame mode using a 64 × 64 digital matrix over 10–12 min and the LVEF was calculated as previously described (*21*).

Biodistribution Protocol

Fluorine-18-fluorodeoxyglucose (0.20 mCi) was injected intravenously in the control group (n = 16), 6-wk treatment group (n = 6); 8-wk treatment group (n = 5); 9-wk treatment group (n = 6); and 10-wk treatment group (n = 3). Some of the animals were simultaneously injected with ^{125}I-BMIPP (0.005 mCi); controls (n = 8), 9-wk group (n = 6) and 10-wk group (n = 3). Technetium-99m-MIBI (30 mCi) was administered to controls (n = 8); 6-wk group (n = 4); 8-wk group (n = 5); and 9-wk group (n = 4). Gated blood pool images were recorded for the controls (n = 13); 6-wk group (n = 6); 8-wk group (n = 6); and 9-wk group (n = 5).

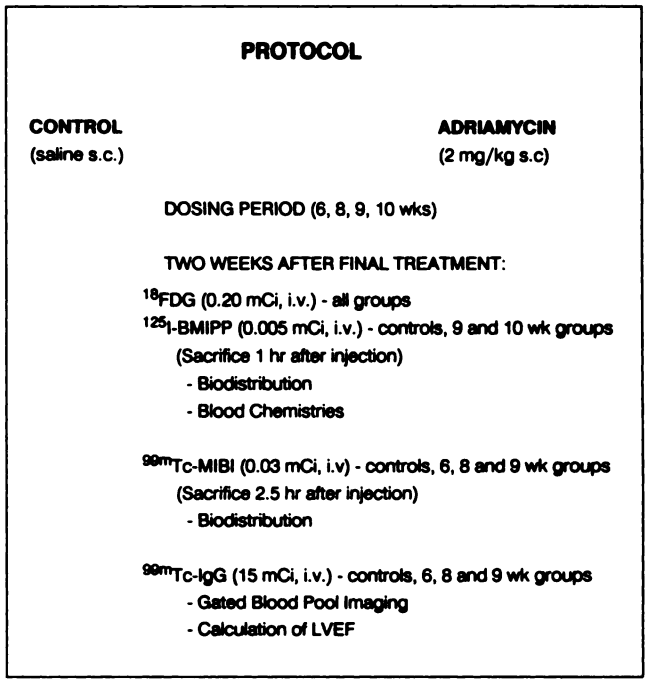

FIGURE 1. Study protocol.

The rats were killed at 2.5 hr after injection of ^{99m}Tc-MIBI and at 1 hr after injection of ^{18}F-FDG and ^{125}I-BMIPP. Radioactivity in the whole heart was measured with a well-type scintillation counter and tracer accumulation was expressed as %kgID/g. The hearts were then divided into; right ventricular wall, septum and left ventricular free wall and the regional distribution of radioactivity was determined. Serum BUN, glucose, albumin, triglycerides and cholesterol were measured from venous blood samples obtained at the time of sacrifice.

Statistical Analysis

All results were expressed as mean ± s.d. Tracer accumulation in the various groups were compared with unpaired t-tests corrected for multiple comparisons (p values of less than 0.05 were defined as statistically significant).

RESULTS

No mortality occurred in the control, 6-wk and 8-wk groups, however, 60% in the 9-wk group and 82% of the 10-wk group died during the treatment period. The average body weight in the 10-wk group was increased compared to controls due to pleural effusions and ascites (Table 1). Myocardial weight was significantly decreased in the 8-wk, 9-wk and 10-wk groups. Pleural effusion and ascites were observed in almost all rats of the 8-wk, 9-wk and 10-wk groups. Blood chemistries demonstrated remarkable hypoalbuminemia, hypertriglycemia and hypercholesteremia indicative of a nephrotic syndrome in the adriamycin treatment groups (Table 2). These abnormalities progressed in a dose-dependent manner, resulting in severe azotemia.

TABLE 1
Necropsy Findings

	No. of rats	Body weight (g)	Heart (g)	Pleural effusion	Ascites
Control	23	344 ± 15	0.86 ± 0.05	0/23	0/23
Adriamycin					
6-wk dose	10	351 ± 24	0.83 ± 0.05	0/10	0/10
8-wk dose	11	349 ± 23	0.81 ± 0.08*	11/11†	8/11†
9-wk dose	10	358 ± 41	0.77 ± 0.11†	10/10†	9/10†
10-wk dose	3	367 ± 20*	0.64 ± 0.06‡	3/3†	3/3†

*$p < 0.05$, †$p < 0.01$ and ‡$p < 0.001$ compared to controls.

Radionuclide Angiography

There were no differences in left ventricular wall motion between controls and the 6-wk group (Fig. 2). However, left ventricular wall motion was significantly reduced in the 8-wk group and more markedly reduced in the 9-wk group. LVEF did not differ between controls and the 6-wk group (81.4% ± 6.3% versus 78.0% ± 4.8%; p = ns) (Fig. 3). LVEF markedly decreased in the 8-wk group (43.1% ± 10.1%; $p < 0.001$). In the 9-wk group, the decrease was even greater (27.6% ± 13.4%; $p < 0.001$).

Technetium-99m-MIBI Accumulation in the Myocardium

Technetium-99m-MIBI accumulation (%kgID/g) in the whole heart at 2.5 hr after injection did not significantly differ between controls (1.29% ± 0.04%) and the 6-wk group (1.34% ± 0.07%), 8-wk group (1.15% ± 0.19%) or 9-wk group (1.20% ± 0.2%) (Fig. 4). The regional distribution of perfusion was homogeneous in the control animals and in all adriamycin treatment groups.

Fluorine-18-Fluorodeoxyglucose Accumulation in the Myocardium

Fluorine-18-fluorodeoxyglucose accumulation (%kgID/g) in the hearts of adriamycin treated animals decreased progressively compared to controls (Fig. 5); controls: 2.19% ± 0.38%; 6-wk group: 1.47% ± 0.42% ($p < 0.01$); 8-wk group: 1.22% ± 0.27% ($p < 0.001$); 9-wk group: 0.69% ± 0.56% ($p < 0.001$); and 10-wk group: 0.50% ± 0.08% ($p < 0.001$). The regional distribution of ^{18}F-FDG in the myocardium remained homogeneous in the treated and control animals. Significant decreases in myocardial accumulation of ^{18}F-FDG were observed earlier than reductions in LVEF (Fig. 6).

Iodine-125-BMIPP Accumulation in the Myocardium

Myocardial ^{125}I-BMIPP accumulation (%kgID/g) was significantly reduced in the 9-wk and 10-wk groups compared to the controls (Fig. 7); controls: 0.38% ± 0.05%; 9-wk group: 0.20% ± 0.04% ($p < 0.001$); and 10-wk group: 0.19% ± 0.06% ($p < 0.001$). Significant effects of adriamycin treatment on regional uptake were not detected. There was a good correlation between myocardial accumulation of ^{125}I-BMIPP and ^{18}F-FDG in controls, 9-wk and 10-wk groups in which the two radiopharmaceuticals were injected at the same time (Fig. 8). The decrease of ^{125}I-BMIPP uptake was well correlated with the decrease in ^{18}F-FDG accumulation. However, the decrease in myocardial accumulation was greater for ^{18}F-FDG than for ^{125}I-BMIPP; 31.6% ± 25.4% of control versus 53.7% ± 9.8% of control (p = ns) in the 9-wk group; 22.6% ± 3.5% of control versus 49.5% ± 15.3% of control ($p < 0.05$) in the 10-wk group.

DISCUSSION

Treatment with adriamycin (2 mg/kg) for 6 wk subcutaneously once a week had no discernible effect on ventricular function (control: 81.4% ± 6.3% versus treated: 78.0% ± 4.8%, p = ns). Two additional weeks of treatment, however, resulted in a marked reduction in ventricular function (43.1% ± 10.1%). Additional therapy resulted in further reduction in ejection fraction. Myocardial accumulation of the glucose analog ^{18}F-FDG was decreased to

TABLE 2
Blood Chemistry

	BUN (mg/dl)	Glucose (mg/dl)	Albumin (g/dl)	Triglyceride (mg/dl)	Cholesterol (mg/dl)
Control (n = 8)	15 ± 2	153 ± 13	1.6 ± 0.1	58 ± 20	66 ± 13
Adriamycin					
6 wk (n = 6)	15 ± 6	139 ± 15	0.8 ± 0.3†	251 ± 104*	244 ± 82‡
8 wk (n = 5)	27 ± 9*	140 ± 16	0.2 ± 0.1‡	350 ± 204†	446 ± 139‡
9 wk (n = 6)	65 ± 53	157 ± 42	0.3 ± 0.1‡	183 ± 296	376 ± 152‡
10 wk (n = 3)	139 ± 2	132 ± 18	0.1 ± 0.0‡	69 ± 39	431 ± 42‡

*$p < 0.05$, †$p < 0.01$ and ‡$p < 0.001$, compared to controls.

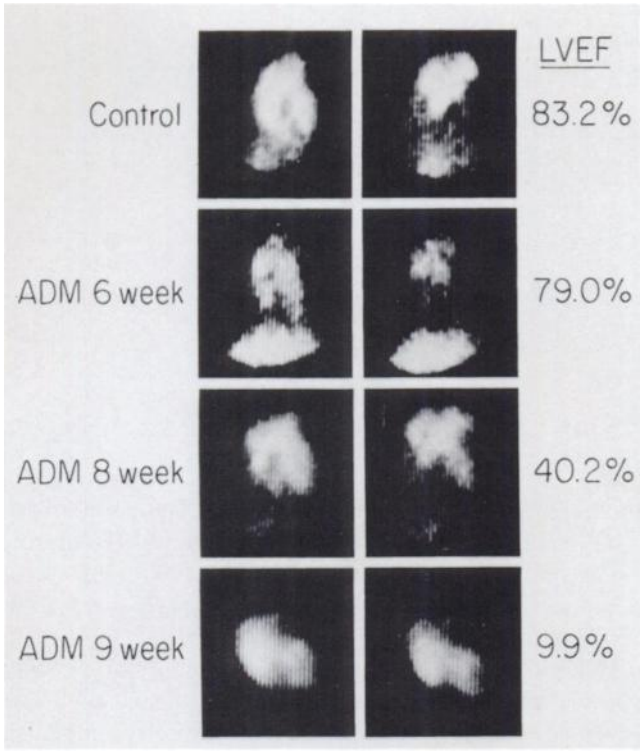

FIGURE 2. Representative gated blood pool images from each adriamycin treatment group (end-diastolic image on left and end-systolic image on right). Normal wall motion was present in the 6-wk group. Left ventricular wall motion was reduced in the 8-wk group. Left ventricular wall motion markedly impaired in the 9-wk group. ADM = adriamycin.

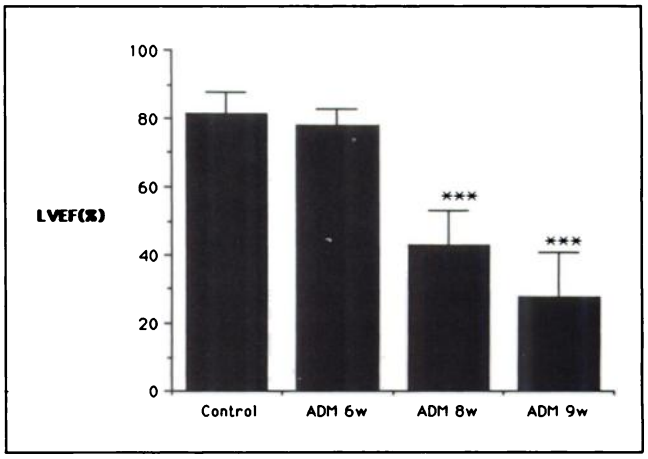

FIGURE 3. Progression of left ventricular dysfunction. The LVEF was normal in the 6-wk group, abruptly decreased in the 8-wk group, and further decreased in the 9-wk group (***$p < 0.001$, compared to controls).

66.9% of control in the 6-wk group. Additional therapy resulted in further reduction of myocardial ^{18}F-FDG accumulation. By 8 wk, myocardial accumulation was 55.6% of control; 31.6% of control at 9 wk; and 22.6% of control at 10 wk.

These results suggest that a reduction in myocardial glucose utilization may be a more sensitive indicator for detecting adriamycin cardiomyopathy than deterioration of left ventricular function. Although the myocardial accumulation of the fatty acid analog ^{125}I-BMIPP was also decreased in the advanced stages of adriamycin cardiomyopathy and was well correlated with the reduction in ^{18}F-FDG utilization, the reduction in ^{125}I-BMIPP accumulation was not as dramatic. Iodine-125-BMIPP is not metabolized by beta-oxidation, and is trapped in the triglyceride fraction (*22*). Although ^{125}I-BMIPP may not be an ideal tracer of myocardial fatty acid metabolism (*23,24*), myocardial accumulation of this tracer is associated with triglyceride synthesis (*25*), which in part reflects fatty acid utilization. The elevation in circulating triglycerides and the marked alteration in fatty acid metabolism associated with the nephrotic syndrome may have in part reduced the measured alterations in fatty acid accumulation as myopathy progressed in the adriamycin model. Recently, it was reported that myocardial accumulation of ^{125}I-BMIPP is positively correlated with myocardial content of adenosine triphosphate, which is required in the first enzymatic conversion of fatty acids to acyl-CoA, a common intermediate of triglyceride synthesis and beta-oxidation (*26*). As a result, the

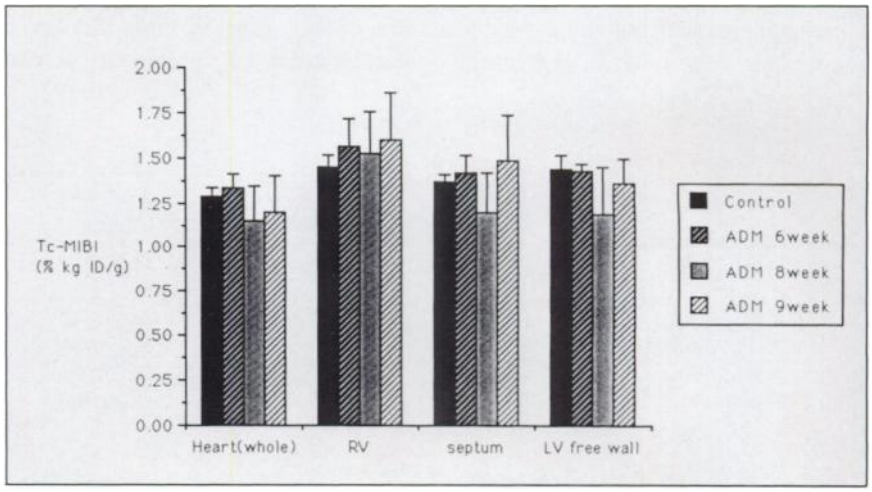

FIGURE 4. Technetium-99m-MIBI accumulation in the heart (%kgID/g). Technetium-99m-MIBI accumulation in hearts of adriamycin treatment animals did not differ from controls. Also, there was no difference in regional myocardial accumulation between controls and the treatment groups.

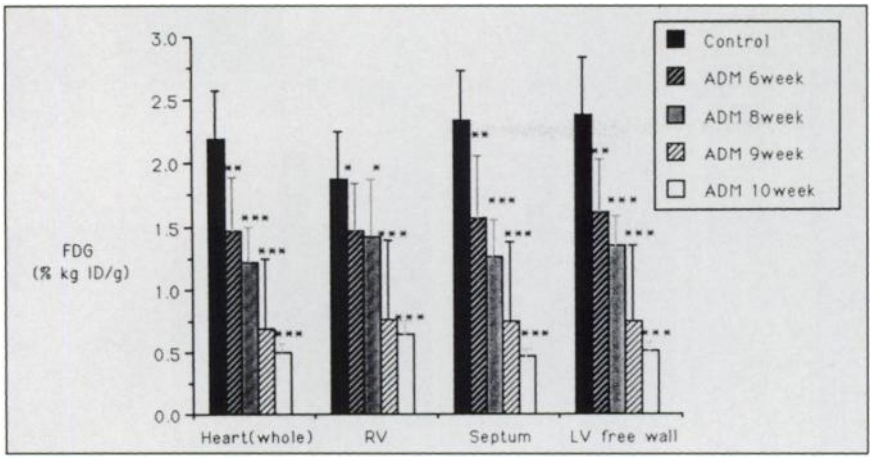

FIGURE 5. Fluorine-18-fluorodeoxyglucose accumulation in the heart (%kgID/g). Fluorine-18-fluorodeoxyglucose accumulation in hearts of adriamycin treated animals progressively diminished compared to controls. Regional myocardial accumulation also showed a dose-dependent decrease (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, compared to controls).

failure to identify a marked change in ^{125}I-BMIPP accumulation may be a reflection of the adriamycin model selected for this study.

Myocardial glucose and fatty acid utilization are influenced by multiple factors, including plasma substrate level, hormonal milieu and myocardial perfusion. In the present investigation, the rats were allowed free access to a standard diet up to the time of the study and there were no significant differences in glucose levels between the treated and control animals. Myocardial blood flow determined with ^{99m}Tc-MIBI did not change significantly compared to controls in any of the adriamycin treatment groups. Although it has been suggested that myocardial retention of ^{99m}Tc-MIBI may reflect viability in addition to perfusion (*27–30*) in coronary artery disease, this issue remains controversial (*31*). Unfortunately, there is currently no data on the value of this tracer as a marker of viability in cardiomyopathy.

Studies of the acute cardiotoxicity of a single injection of adriamycin have demonstrated a slight depression of myocardial oxidation of long chain fatty acids (*32*) and impaired utilization of the fatty acid analog, ^{131}I-15-p-iodophenylpentadecanoic acid (pIPPA) which reflects beta-oxidation (*33*). Acute cardiotoxicity is not equivalent to chronic cardiotoxicity which is a dose-dependent condition, however, the acute cardiovascular effects of adriamycin could be related to the development of chronic cardiotoxicity. We chose to assess myocardial substrate metabolism 2 wk after the final adriamycin treatment in order to minimize the acute effects of adriamycin.

In a study of the chronic cardiotoxicity with ^{131}I-heptadecanoic acid (^{131}I-HA), a mild but significant prolongation in the myocardial half-time of ^{131}I-HA was observed only at high cumulative doses. Also, changes in ejection fraction were observed before there was a significant change in the myocardial half-time of ^{131}I-HA (*34*).

Since we did not study myocardial accumulation of ^{125}I-BMIPP in the 6-wk group (normal LVEF) or the 8-wk group (early decrease in LVEF), it is uncertain whether decreased myocardial ^{125}I-BMIPP accumulation precedes the decrease in LVEF. However, the decrease in ^{125}I-BMIPP accumulation was not as great as the decrease in ^{18}F-FDG accumulation in the 9-wk group which showed a marked reduction in LVEF or in the 10-wk group (the last

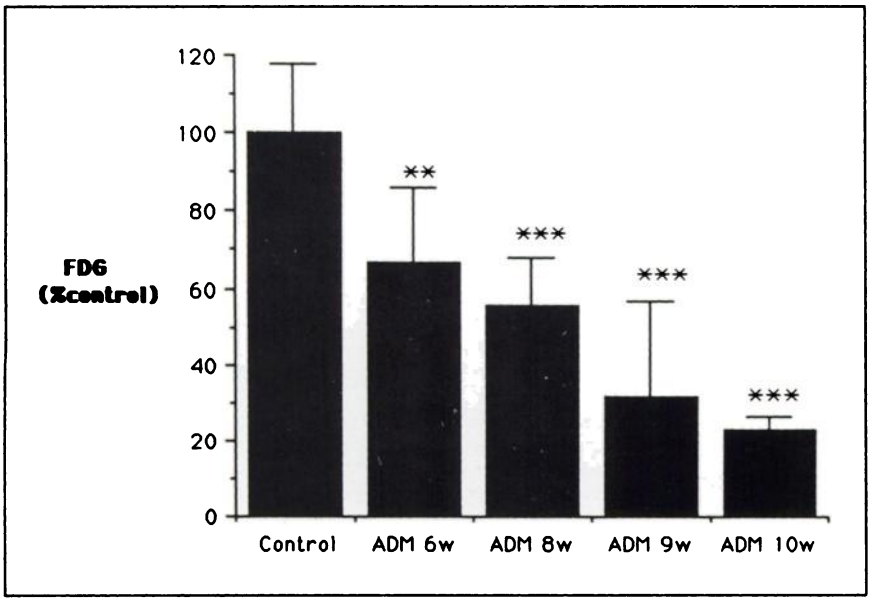

FIGURE 6. Progression of decrease in ^{18}F-FDG accumulation in the myocardium (%kgID/g). Decrease in ^{18}F-FDG accumulation in adriamycin-treated animals appeared earlier than deterioration in LVEF and progressed more linearly (**$p < 0.01$, ***$p < 0.001$, compared to controls).

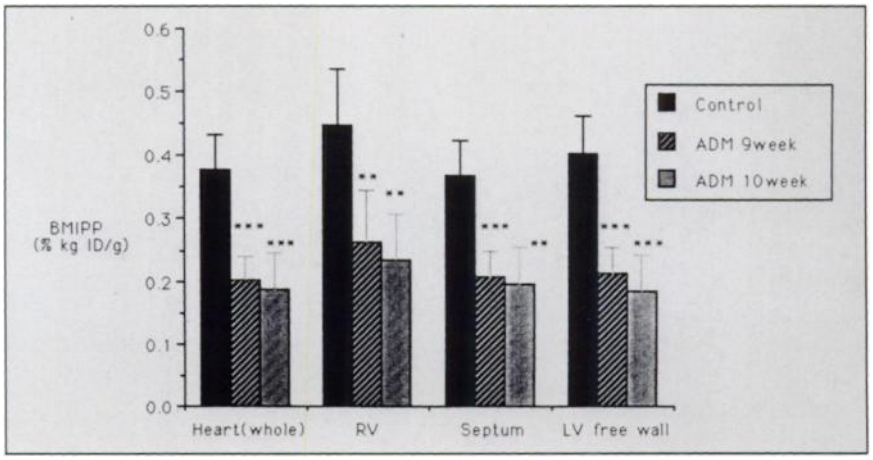

FIGURE 7. Progression of decrease in ^{125}I-BMIPP accumulation in the heart (%kgID/g). ^{125}I-BMIPP accumulation was significantly decreased in the 9-wk and 10-wk groups. There were no effect on regional myocardial accumulation in any group (**p < 0.01, ***p < 0.001, compared to controls).

practical time to make measurements due to the high mortality from cardiac and renal failure).

Impaired myocardial glucose utilization reflected by decreased ^{18}F-FDG accumulation may be a sensitive metabolic marker for adriamycin cardiomyopathy. Several previous studies have suggested that there is increased or normal myocardial glucose utilization in cardiomyopathic hamsters and in patients with congestive cardiomyopathy or heart failure. Since, under the condition of unaltered myocardial perfusion, no single metabolic effect can decrease both ^{18}F-FDG and ^{125}I-BMIPP accumulation, adriamycin probably effects myocardial metabolism at multiple sites. Thus, the decrease in myocardial accumulation of ^{18}F-FDG observed in our study may reflect cytotoxic effects at the myocyte membrane and membrane bound enzymes.

In conclusion, myocardial accumulation of ^{18}F-FDG may be a useful clinical marker for detecting adriamycin cardiotoxicity. It is suggested that both glucose and fatty acid utilization is decreased in adriamycin cardiomyopathy and critical impairments in myocardial energy metabolism occur before mechanical function is substantially reduced.

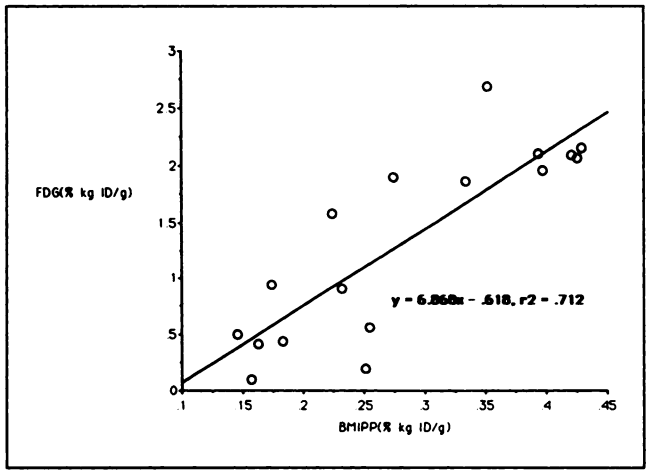

FIGURE 8. Correlation between ^{125}I-BMIPP and ^{18}F-FDG accumulation in the hearts of controls 9 and 10 treated animals. ^{125}I-BMIPP and ^{18}F-FDG were injected at the same time. Decrease in ^{125}I-BMIPP accumulation was well correlated with decrease in ^{18}F-FDG accumulation (r^2 = 0.712, p < 0.001).

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