Effect of Doxorubicin on [ω-I-131]Heptadecanoic Acid Myocardial Scintigraphy and Echocardiography in Dogs

C. B. Styles, A. A. Noujaim, B. I. Jugdutt, T. R. Sykes, G. O. Bain, T. K. Shnitka, and H. R. Hooper

Cross Cancer Institute, University of Alberta, and Surgical and Medical Research Institute, Edmonton, Alberta, Canada

The effects of serial treatment with doxorubicin on dynamic myocardial scintigraphy with [ω-I-131]heptadecanoic acid (I-131 HA), and on global left-ventricular function determined echocardiographically, were studied in a group of nine mongrel dogs. Total extractable myocardial lipid was compared postmortem between a group of control dogs and doxorubicin-treated dogs. A significant and then progressive fall in global LV function was observed at a cumulative doxorubicin dose of 4 mg/kg. A significant increase in the myocardial $t_{1/2}$ of the I-131 HA was observed only at a higher cumulative dose, 10 mg/kg. No significant alteration in total extractable myocardial lipids was observed between control dogs and those treated with doxorubicin. Our findings suggest that the changes leading to an alteration of myocardial dynamic imaging with I-131 HA are not the initiating factor in doxorubicin cardiotoxicity.

J Nucl Med 24: 1012–1018, 1983

Cardiotoxicity is the major dose-limiting complication in the treatment of malignancy with doxorubicin or other anthracycline drugs. The most serious manifestation of this toxicity is chronic congestive heart failure, often fatal. The probability of this occurring appears to be dose related (*1*), hence the practice of withholding further treatment with doxorubicin after the cumulative dose of 550 mg/m^2 is reached (*1,2*). However, some patients do not suffer a clinically significant degree of cardiotoxicity even at this dose, and may benefit from further treatment with doxorubicin. In addition, other patients who have been exposed to additional risk factors—such as previous radiotherapy to the mediastinum, cyclophosphamide administration, advanced age, previous hypertension, or other cardiac disease—have an increased risk of developing congestive cardiac failure before reaching the cumulative dose of 550 mg/m^2 of doxorubicin (*2,3*).

Clinical cardiac failure due to doxorubicin responds poorly to treatment, and the mortality from this condition is approximately 50% (*2,3*). Considering this, various monitoring techniques have been suggested for detecting early doxorubicin cardiotoxicity, such as radionuclide left-ventricular ejection fraction studies (LVEF) (*4,5*), systolic time intervals, electrocardiography, echocardiography (*6–8*), and cardiac biopsy (*9*). Functional imaging of the heart, e.g., radionuclide LVEF and echocardiography, has been reported to provide a noninvasive index of the onset of doxorubicin cardiotoxicity (*5–8*).

The mechanism of chronic doxorubicin cardiotoxicity is not well understood. Proposed explanations include membrane lipid peroxidation due to enhanced free-radical formation (*10,11*), inhibition of enzymes involved with cell respiration (*12*), altered flux of calcium within myocytes (*13*), and interference with DNA transcription and subsequent protein synthesis (*14*). If alterations of the cell membrane or mitochondrial dysfunction are important factors in the genesis of chronic doxorubicin cardiotoxicity, changes in myocardial metabolism may precede the observed changes in cardiac function and so provide a useful clinical marker of car-

Received Feb. 22, 1983; revision accepted June 20, 1983.

For reprints contact: Dr. C. B. Styles, Dept. of Nuclear Medicine, Cross Cancer Institute, 11560 University Ave., Edmonton, Alberta, Canada T6G 1Z2.

diotoxicity.

We examined this possibility in dogs receiving doxorubicin on a weekly schedule. Serial dynamic myocardial imaging with [ω-I-131]heptadecanoic acid (I-131 HA) was performed in conjunction with serial ultrasonic assessment of global cardiac function. In addition, postmortem myocardial studies with light and electron microscopy were performed, along with assays of total myocardial lipids.

MATERIALS AND METHODS

Animals and doxorubicin administration. Experiments were performed on nine healthy mongrel dogs, mean age 2–6 yr and mean weight 20.6 kg. Before treatment with doxorubicin, baseline echocardiographic measurements and myocardial scintigrams with I-131 HA were recorded. In four of the dogs the scintigrams were degraded by malfunction of computer data storage. To form the control group, four additional healthy animals of similar age and weight were studied. Weekly intravenous infusions of doxorubicin hydrochloride were given at a maximum dose of 1 mg/kg according to the hematological tolerance of each of the nine dogs [modification of the technique of Van Vleet et al. (*15*)]. Echocardiography and I-131 HA dynamic myocardial imaging were repeated at five weekly intervals. After death (n = 8) or sacrifice (n = 1), the hearts and lungs were examined and a transmural block from the anterolateral wall of the left ventricle (LV) was sampled. This was divided into three portions for light microscopy, electron microscopy, and lipid assays.

ELECTRON MICROSCOPY, LIGHT MICROSCOPY, AND ASSAY OF MYOCARDIAL LIPIDS

For electron microscopy, 1 to 2 mm cubes were first fixed for 24 hr in 4% glutaraldehyde in 0.1 *M* cacodylate buffer at 4°C. The tissues were then fixed in 1% osmium tetroxide for 2 hr, followed by dehydration through a graded ethanol series and embedding in resin.* The specimens were sectioned and stained with uranyl acetate and lead citrate.

For light microscopy, blocks of 3 cm full thickness were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E) for histopathologic study. The degree of observed vacuolar degeneration was graded using the method of paired comparisons for ranking (*16*).

In seven of the nine experimental animals, a separate specimen was frozen at −20°C for subsequent lipid analysis. To provide control values for this assay, heart tissue was obtained from five healthy mongrel dogs of age and weight similar to the experimental animals. Full-thickness specimens of the left-ventricular myocardium, weighing 1 g, were trimmed of visible epicardial fat, cut into small (2 mm) cubes, frozen in liquid nitrogen, and then pulverized with a mortar and pestel. Accurately weighed aliquots were thoroughly agitated for 30 min with 20 ml of chloroform/methanol (2:1, v/v) at room temperature (*17*). The lipid extract was separated from the myocardial tissue by sintered-glass filtration into a preweighed vial. After two washings, in each of 10 ml of the chloroform/methanol mixture, the solvent was evaporated, leaving the lipid residue. The residue and the vial were then weighed and the percentage of extractable myocardial lipid calculated.

ECHOCARDIOGRAPHIC RECORDINGS

M-mode echocardiograms were recorded on an ultrasonograph equipped with a strip-chart recorder, with the dogs anesthetized (pentobarbital, 30 mg/kg i.v.) and lying in the left lateral position. The chests were shaven. The transducer (2.25 MHz, crystal 13 mm diam) was positioned in the fourth left interspace, parasternally, so as to obtain optimal traces of the mitral valve; it was then rotated slightly inferiorly to identify the left-ventricular chamber including the mitral chordae tendineae (*6*). The position of the transducer was noted for use in subsequent serial studies. The electrocardiogram (Lead II) was recorded simultaneously with the echocardiogram for definition of end-diastole (peak of R wave) and end-systole (peak of T wave). End-diastolic and end-systolic dimensions of the left ventricle were measured and ejection fractions (EF) calculated (*18*):

$$EF(\%) = \frac{(\text{LV i.d.}_{\text{diast.}})^3 - (\text{LV i.d.}_{\text{syst.}})^3}{(\text{LV i.d.}_{\text{diast.}})^3} \times 100\%$$

SYNTHESIS OF [ω-I-131]HEPTADECANOIC ACID

Two hundred and twenty-five μg of 17-Br-[17-Br]-heptadecanoic acid were reacted with 10.8 mCi (400 MBq) of $Na^{131}I$ (injection grade) in 200 μl of acetone. Before the reaction, the fatty acid and I-131 solutions were dried under vacuum for 12 hr to remove the aqueous phase. The acetone was also refluxed over $CaCl_2$ and P_2O_5 to remove all traces of water. The reaction was carried out at 70–72°C for 2 hr. Unreacted iodide was removed by evaporating the acetone, redissolution of the mixture in dried chloroform, and passage of the latter solution through a mini silica-gel column. Radiochemical purity of the final product was confirmed using both Whatman MK_6F silica-gel chromatography plates (solvent system chloroform:ethanol, 12:1) and Whatman $MKC_{18}F$ reverse-phase chromatography plates (solvent system ethanol/water/acetic acid, 90:9.5:0.5). Labeling efficiency was ~70% and the purity greater than 97%.

The labeled fatty acid was bound to canine serum after evaporation of the chloroform and redissolution in 100 μl ethanol. Three milliliters of dog serum were added and

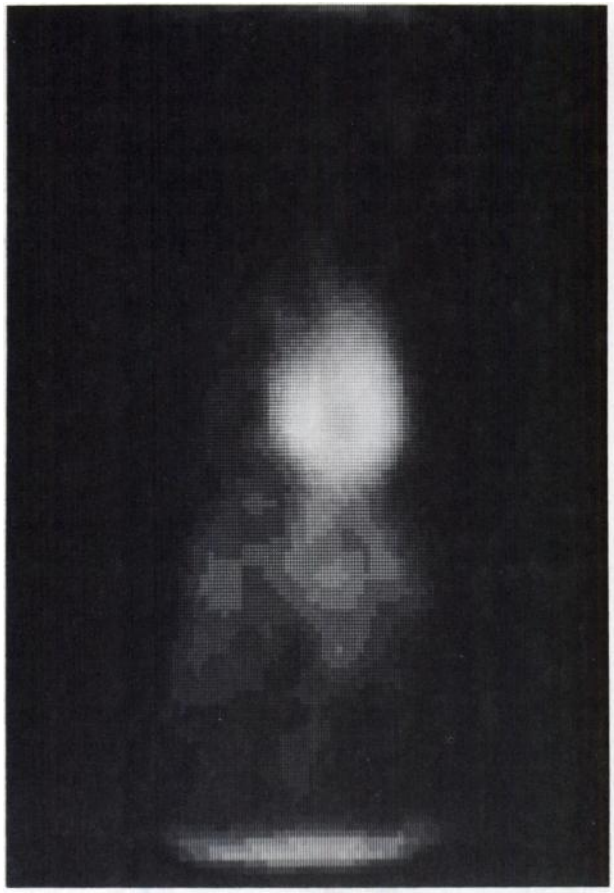

FIG. 1. Anterior view of dog heart, demonstrating concentration of [ω-I-131]heptadecanoic acid in myocardium.

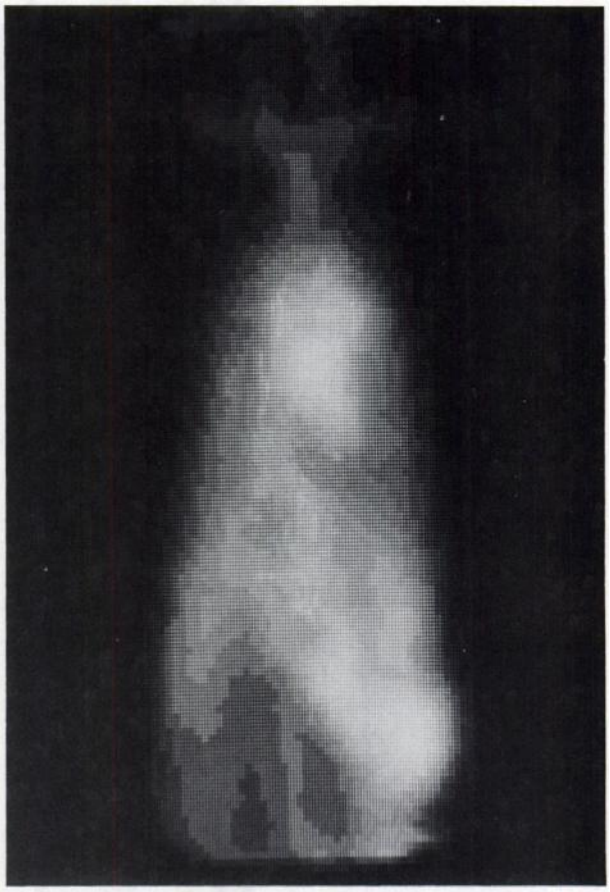

FIG. 2. Anterior view of dog demonstrating Tc-99m RBC blood-pool distribution in chest and abdomen. Orientation same as in Fig. 1.

the mixture incubated at 37°C for 30 min. A final filtering step was carried out through a 0.22-μm filter before use. Recoveries were normally greater than 95%. Each dog was injected with 1.5–2.2 mCi (~40–60 MBq) of I-131-labeled fatty acid.

SCINTIGRAPHIC IMAGING AND COMPUTER ANALYSIS

The dogs were fasted for 12 hr, and before imaging they were anesthetized with intravenous pentobarbital, 30 mg/kg. Scintigraphy was performed using a large-field-of-view gamma camera equipped with a medium-energy parallel-hole collimator. Imaging used a 15% window over the 364-keV peak. The camera was interfaced to a digital computer. The animal lay supine, and anterior imaging of the dog's chest was commenced upon the injection of the iodo-fatty acid. Data were collected in a 64 × 64 matrix at one frame per minute for 40 min. At the completion of 30 min, a second i.v. injection of sodium iodide, of similar activity to the I-131 fatty acid, was given for the purpose of background correction (*19*). A modified protocol was used in three dogs, which were imaged for 75 min rather than 40 min, with the injection of the $Na^{131}I$ occurring after 65 min. This was done to examine better the possibility of a biexponential clearance of radioactivity from the myocardium.

Observation of the computer-stored images permitted the identification of the left-ventricular (LV) myocardium (Fig. 1). For subtraction of blood and interstitial background, a region immediately superior to the observed LV myocardium was chosen. A Tc-99m(Sn) pyrophosphate blood-pool image, using the in vivo technique of RBC labeling and performed at the same time using dual-nuclide techniques, is shown in Fig. 2 for comparison. The LV and the background regions of interest are shown in Fig. 3, together with the time-activity curves generated for these regions.

One can appreciate from Figs. 1–3 the importance of blood background activity in the LV region of interest when one is attempting to examine only the myocardial activity. Using the relative incremental increase of activity in these two regions following the injection of $Na^{131}I$ as an indicator of the contribution from the blood-pool and interstitial activity, a corrected myocardial time-activity curve was generated [method of Freundlieb et al. (*19*), Fig. 4]. Analysis of this myocardial time-activity curve revealed a single exponential release of activity from the myocardium after peak activity between 5 and 10 min. The half-time of activity ($t_{1/2}$) in the heart has been proposed as a marker of

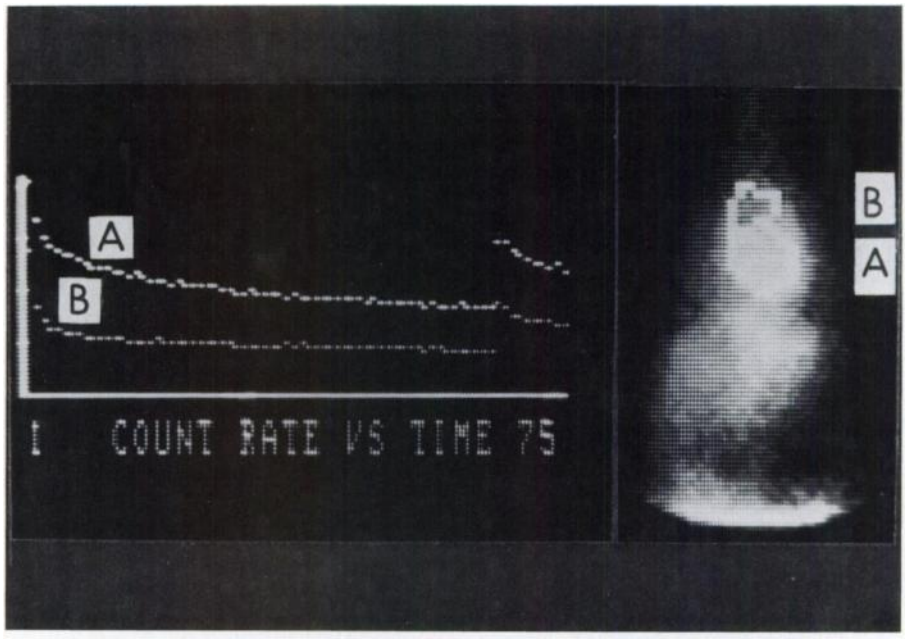

FIG. 3. Composite demonstration of myocardial (A) and background (B) ROIs used to generate time-activity curves, which are shown plotted up to 75 min. Curve B is multiplied by calculated correction factor, 1.3, then subtracted from Curve A, to derive myocardial time-activity curve.

cardiac fatty-acid metabolism (*19*), and is the scintigraphic parameter studied in this protocol.

RESULTS

Histopathologic findings. Of the nine dogs studied, one died after a cumulative dose of doxorubicin of 5.7 mg/kg was achieved. The remaining eight dogs survived to receive a cumulative dose of at least 10 mg/kg, with the maximum administered cumulative dose before death being 15.6 mg/kg. Portmortem in three of the animals revealed a blood-stained pericardial effusion. No focal macroscopic abnormality was observed in the myocardium, coronary vessels, endocardium, or valve structures in any of the dogs. Macroscopic examination of the lungs revealed varying degrees of pulmonary congestion, edema, and bronchopneumonia. Vacuolar degeneration was the major abnormality in LV muscle stained with H & E. On electron microscopy, these vacuoles were found to arise from dilated segments of the sarcoplasmic reticulum. The magnitude of this abnormality increased with the cumulative dose of doxorubicin administered. The distribution of this vacuolar degeneration within the LV myocardium was patchy. Examples of the light- and electron-microscopic features are shown in Figs. 5 and 6.

Echocardiographic findings. The changes in global ejection fraction at varying doses of doxorubicin are

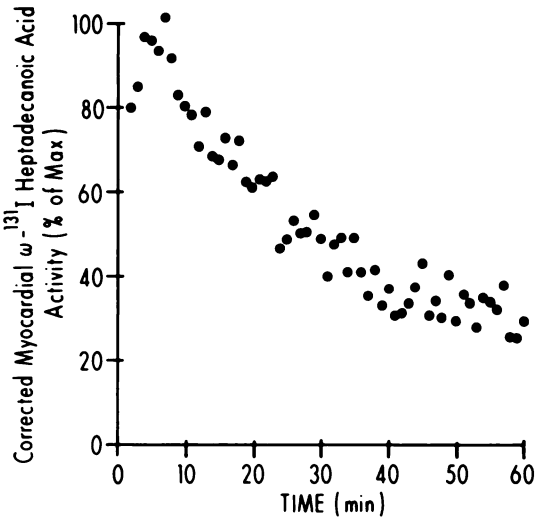

FIG. 4. Background-corrected time-activity curve for myocardial [ω-I-131]heptadecanoic acid. Myocardial activity is expressed as percentage of maximum.

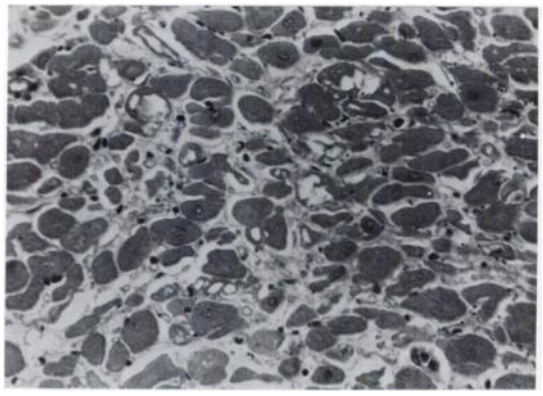

FIG. 5. Optical photomicrograph showing vacuolar degeneration of several myocardial fibres. Hematoxylin and eosin. Original magnification ×100.

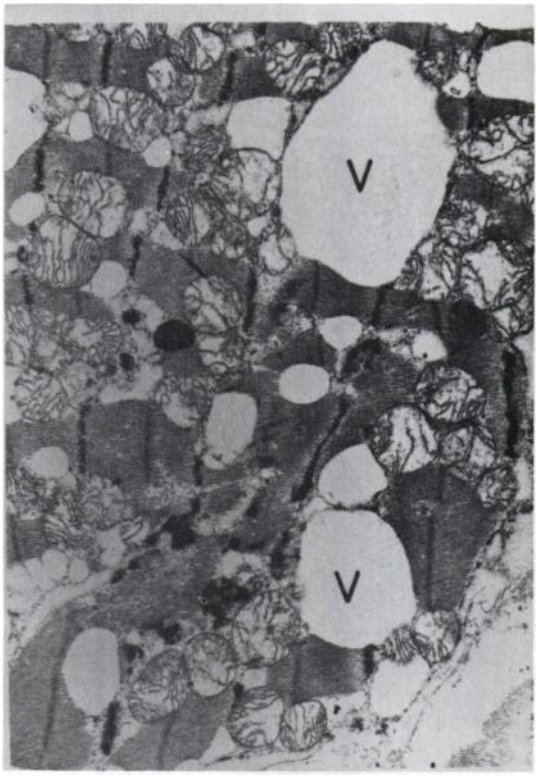

FIG. 6. Electron microscopy shows presence of numerous large and small vacuoles (v) arising from dilated segments of sarcoplasmic reticulum. Mitochondrial swelling is due to delay in fixation. Original magnification ×2800.

presented in Fig. 7. A significant decrease in ejection fraction was detected after a cumulative doxorubicin dosage of 4 mg/kg ($p < 0.05$ by Student's t-test). This deterioration in LV function continued with cumulative doses of 8 mg/kg and 11–12 mg/kg. At the final level tested, the ejection fraction was 57% ± 9 (mean ± standard deviation of group) and represents a 24% decrease from the control values of 75% ± 5.

Scintigraphic findings. The $t_{1/2}$ of the calculated myocardial activity was determined using a single exponential fit following peak activity. In three studies this curve was generated for 65 min. Analysis of these myocardial time-activity curves using an autoan-nonlin commercially available program,† identified only single exponential clearance of myocardial activity after the peak.

The results of scintigraphy are summarized in Fig. 8. The $t_{1/2}$ of the I-131 radioactivity in the myocardium for dogs before receiving doxorubicin averaged 14.0 ± 2.9 min. It averaged 14.6 ± 1.5 min (N.S.) when the group had received a cumulative dose of doxorubicin between 1–2 mg/kg. At a dose of 5 mg/kg the $t_{1/2}$ averaged 14.7 ± 2.6 min (N.S.), and at a cumulative dose of 10 mg/kg the $t_{1/2}$ was 17.6 ± 2.7 min. The changes were significant ($p < 0.05$ by Student's t-test) only with the 10 mg/kg cumulative dose; the other changes were not. No significant differences were observed in peak myocardial activity or time to peak in animals with or without doxorubicin treatment.

Myocardial lipid assays. The total extractable myocardial lipid averaged 5.22% ± 0.42 by weight in the controls and 4.91% ± 0.88 in the doxorubicin-treated dogs, with no statistically significant difference ($p > 0.05$) between the two groups.

DISCUSSION

The deterioration in global LV ejection fraction by M-mode echocardiography in our study supports previously reported findings in patients receiving doxorubicin (*6*). Postmortem cardiac histology demonstrated vacuolar degeneration, a typical feature associated with doxorubicin cardiotoxicity (*15*). The degree of myocardial vacuolar degeneration correlated with the cumulative dose of doxorubicin.

In the fasting state, the healthy heart derives nearly 70% of its energy requirements from the beta oxidation of long-chain fatty acids (*20*). These fatty acids are extracted from the coronary circulation by the myocardium, taken up into the cytoplasm, transferred across the mitochondrial membrane via the carnitine shuttle, and catabolized. With the terminally iodinated fatty acids, such as [ω-I-131]heptadecanoic acid, it has been proposed that when the process of beta oxidation reaches the C_1 stage, either the iodine or the iodinated acyl fragment is liberated and returns to the circulation (*21*). Machulla et al. (*23*) observed a similar time course of myocardial activity in mice injected with either I-131 HA or C-11-labeled palmitate. In the healthy dog, where precordial clearance studies were performed, a close parallel was observed between I-131 HA, C-11 oleic acid, and C-11 stearic acid in the first 3–10 min following intravenous injection (*24*). These observations suggest that the myocardial metabolism of the terminally iodinated

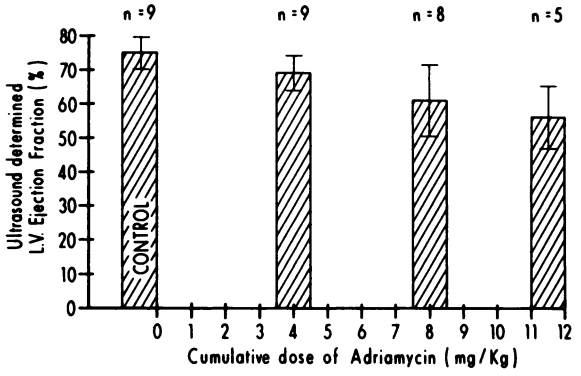

FIG. 7. Histogram (group mean ± s.d.) demonstrating EF determined by ultrasound in animals with no exposure to doxorubicin and at various cumulative doses. Statistically significant difference ($p < 0.05$) between treated and untreated groups was observed at all dosage levels.

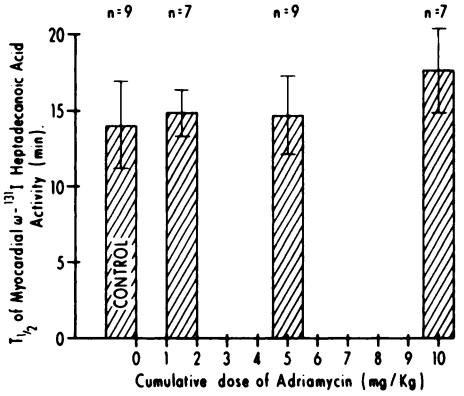

FIG. 8. Histogram (group mean ± s.d.) demonstrating $t_{1/2}$ of myocardial [ω-I-131]heptadecanoic acid, in animals with no exposure to doxorubicin and under various cumulative doses. Statistically significant difference ($p < 0.05$) between treated and untreated group was observed only at highest dosage level.

fatty acids models that of the natural fatty-acid substrate.

Experiments in isolated, perfused rabbit hearts, using C-11 palmitate and performed under controlled conditions, have demonstrated that the changes in the rate of clearance of the injected radioactivity from the heart are dependent on cardiac metabolism (*25,26*). In the healthy dog the myocardial half-time ($t_{1/2}$) for C-11 palmitate has been measured as 11.6 ± 1.0 min and rose during experimentally produced ischemia to 15.8 ± 4.2 min (*27*). Using I-123 HA and correcting for free I-123, the myocardial $t_{1/2}$ for this tracer in the healthy dog has been measured as 13.4 ± 1.4 min, and in sites of coronary occlusion as 25.1 ± 2.6 min and 22.6 ± 1.8 min with 5 min and 90 min of ischemia, respectively (*28*). Using similar methods in the human, the myocardial $t_{1/2}$ for I-123 HA has been calculated as 27.5 ± 3.0 min in healthy subjects and elevated (46.4 ± 7.1 min) in ischemic regions in patients with angina (*29*). Peak concentration in these ischemic regions was reduced (*29*). Studies of human myocardial concentration using C-11 palmitate have indicated a $t_{1/2}$ of 27 min (*30*). These animals and human data support the use of terminally iodinated long-chain fatty acids as markers of fatty acid myocardial metabolism in both health and disease.

Feinendegen et al. (*21*) and Hock et al. (*22*) have observed a prolongation of the $t_{1/2}$ of iodinated fatty acid within the myocardium in a group of patients with congestive cardiomyopathy. This finding parallels the observation of a significant prolongation in the $t_{1/2}$ of the iodofatty acid myocardial activity in dogs receiving doxorubicin in the latter phase of this study. It is tempting to propose that this reflects an altered rate of myocardial beta oxidation. However, such changes may represent the influence of altered myocardial lipid-pool sizes, or could be due to an altered rate of washout of the free iodine or small iodine fragments from the myocardium due to the altered cardiac hemodynamics influenced by the worsening cardiomyopathy, (*30–32*). Our failure to observe a significant alteration in extractable lipid from the dog's heart suggests that the $t_{1/2}$ of the myocardial activity in this experiment was not due to increased lipid pools. Nevertheless, an alternative explanation is that selective lipid levels might have been altered, although not detected by our assay of total extractable lipids. In addition, our assay might not be able to detect alterations in the shift of lipids between pools of differing metabolic activity.

The changes in global ejection fraction measured with echocardiography were observed earlier than a significant change in the $t_{1/2}$ of the myocardial activity. This suggests that the metabolic or circulatory alterations detected with scintigraphy are not the initiating events in the cardiac dysfunction.

Dudczak et al. (*33*), have reported a biexponential clearance of myocardial activity in calves following the intracoronary injection of I-131 HA and in humans injected intravenously with the same tracer. In three of our studies we were able to obtain myocardial iodofatty-acid time-activity curves for 65 min. In this limited number we could not identify a biexponential decrease in myocardial activity.

In summary, we detected myocardial changes using iodoheptadecanoic acid scintigraphy. Echocardiographic cardiac evaluation appeared to be more sensitive in detecting alterations in cardiac function due to doxorubicin in our dog model. It would be of interest to examine both fatty-acid cardiac imaging and global cardiac function in patients undergoing treatment with doxorubicin. It is not known whether a finding similar to that in the dog model will be observed in humans, or whether the alteration of the $t_{1/2}$ of the iodofatty acid in the heart might provide a clinically useful threshold for assessing doxorubicin cardiotoxicity. The factors influencing the myocardial residence time of the iodofatty acids in myocardial disease remain to be studied.

FOOTNOTES

* Epon 812.

† C. N. Metzler, NONLIN—a computer program for parameter estimation in nonlinear situations. The Upjohn Co. Biostats Dept., Michigan, 1969.

ACKNOWLEDGMENTS

We are indebted to Miss C. Turner and Mr. D. Abrams for radiopharmaceutical assistance; to Dr. M. Jamalli for his help with pharmacokinetic analysis; to Mr. T. Germaine and Mrs. M. Reisel for technical assistance, and to Mrs. Mary Laschowski for typing the manuscript.

This work was supported by the Canadian Cancer Society and the Alberta Cancer Board, Edmonton, Alberta.

REFERENCES

1. LEFRAK EA, PITHA J, ROSENHEIM S, et al: A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer* 32:302-314, 1973
2. CHLEBOWSKI RT: Adriamycin (doxorubicin) cardiotoxicity: a review. *West J Med* 131:364-368, 1979
3. VON HOFF DD, LAYARD MW, BASA P, et al: Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 91:710-717, 1979
4. SINGER JW, NARAHARA KA, RITCHIE JL, et al: Time- and dose-dependent changes in ejection fraction determined by radionuclide angiography after anthracycline therapy. *Cancer Treat Rep* 62:945-948, 1978
5. ALEXANDER J, DAINIAK N, BERGER HJ, et al: Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. *N Engl J Med* 300:278-283, 1979
6. BLOOM R, BINI RM, CONSTANCE MW, et al: Echocardiography in adriamycin cardiotoxicity. *Cancer* 41:1265-1269, 1978
7. EWY GA, JONES SE, FRIEDMAN MJ, et al: Noninvasive cardiac evaluation of patients receiving adriamycin. *Cancer Treat Rep* 62:915-922, 1978
8. RAMOS A, MEYER RA, KORFHAGEN J, et al: Echocardiographic evaluation of adriamycin cardiotoxicity in children. *Cancer Treat Rep* 60:1281-1284, 1976
9. BILLINGHAM ME, MASON JW, BRISTOW MR, et al: Anthracycline cardiomyopathy monitored by morphologic changes. *Cancer Treat Rep* 62:865-872, 1978
10. D'ALESSANDRO N, DUSONCHET L, CROSTA L, et al: Does catalase play a role in adriamycin induced cardiotoxicity? *Pharmacol Res Commun* 13:205-211, 1981
11. MYERS CE, MCGUIRE WP, LISS RH, et al: Adriamycin: the role of lipid peroxidation in cardiac toxicity and tumor response. *Science* 197:165-167, 1977
12. IWAMOTO Y, HANSEN IL, PORTER TH, et al: Inhibition of coenzyme Q_{10}-enzymes, succinoxidase and NADH-oxidase, by adriamycin and other quinones having antitumor activity. *Biochem Biophys Res Commun* 58:633-638, 1974
13. REVIS NW, MARUSIC N: Effects of doxorubicin and its aglycone metabolite on calcium sequestration by rabbit heart, liver and kidney mitochondria. In *Life Sciences*. Vol 25, Pergamon Press, 1979, pp 1055-1064
14. ZÄHRINGER J, HÖFLING B, RAUM W, et al: Effect of adriamycin on the polyribosome and messenger-RNA content of rat heart muscle. *Biochem Biophys Acta* 608:315-323, 1980
15. VAN VLEET JF, FERRANS VJ, WEIRICH WE: Cardiac disease induced by chronic adriamycin administration in dogs and an evaluation of vitamin E and selenium as cardioprotectants. *Am J Pathol* 99:13-42, 1980
16. SHEA SM: The method of paired comparisons in histopathologic ranking. *Arch Pathol* 65:77-80, 1958
17. VAN DER VUSSE GJ, ROEMEN TH, PRINZEN FW, et al: Uptake and tissue content of fatty acids in dog myocardium under normoxic and ischemic conditions. *Circ Res* 50:538-546, 1982
18. POMBO JF, TROY BL, RUSSELL RO, JR: Left ventricular volumes and ejection fraction by echocardiography. *Circulation* 43:480-490, 1971
19. FREUNDLIEB C, HÖCK A, VYSKA K, et al: Myocardial imaging and metabolic studies with [17-^{123}I]iodoheptadecanoic acid. *J Nucl Med* 21:1043-1050, 1980
20. NEELY JR, ROVETTO MJ, ORAM JF: Myocardial utilization of carbohydrate and lipids. *Prog Cardiovasc Dis* 15: 289-329, 1972
21. FEINENDEGEN LE, VYSKA K, FREUNDLIEB C, et al: Non-invasive analysis of metabolic reactions in body tissues, the case of myocardial fatty acids. *Eur J Nucl Med* 6:191-200, 1981
22. HÖCK A, FREUNDLIEB C, VYSKA K, et al: Myocardial imaging and metabolic studies with [17-^{123}I]iodoheptadecanoic acid in patients with idiopathic congestive cardiomyopathy. *J Nucl Med* 24:22-28, 1983
23. MACHULLA HJ, STÖCKLIN G, KUPFERNAGEL CH, et al: Comparative evaluation of fatty acids labeled with C-11, C1-34m, Br-77 and I-123 for metabolic studies of the myocardium: Concise communication. *J Nucl Med* 19:298-302, 1978
24. POE ND, ROBINSON GD, GRAHAM LS, et al: Experimental basis for myocardial imaging with ^{123}I-labeled hexadecanoic acid. *J Nucl Med* 17:1077-1082, 1976
25. GOLDSTEIN RA, KLEIN MS, WELCH MJ, et al: External assessment of myocardial metabolism with C-11 palmitate in vivo. *J Nucl Med* 21:342-348, 1980
26. KLEIN MS, GOLDSTEIN RA, WELCH MJ, et al: External assessment of myocardial metabolism with [^{11}C]palmitate in rabbit hearts. *Am J Physiol* 237:H51-H58, 1979
27. LERCH R, AMBOS H, BERGMANN SR, et al: Localisation of viable, ischemic myocardium by positron-emission tomography with C-11 palmitate. *Circulation* 64:689-699, 1981
28. VAN DER WALL EE, WESTERA G, DEN HOLLANDER W, et al: External detection of regional myocardial metabolism with the radioiodinated hexadecenoic acid in the dog heart. *Eur J Nucl Med* 6:147-151, 1981
29. VAN DER WALL EE, HEIDENDAL GA, DEN HOLLANDER W, et al: Metabolic myocardial imaging with ^{123}I labeled heptadecanoic acid in patients with angina pectoris. *Eur J Nucl Med* 6:391-396, 1981
30. TER-POGOSSIAN MM, KLEIN MS, MARKHAM J, et al: Regional assessment of myocardial metabolic integrity in vitro by positron-emission tomography with ^{11}C-labeled palmitate. *Circulation* 61:242-255, 1980
31. SCHELBERT HR, PHELPS ME, HOFFMAN E, et al: Regional myocardial blood flow, metabolism and function assessed noninvasively with positron emission tomography. *Am J Cardiol* 46:1269-1277, 1980
32. SOBEL BE, WEISS ES, WELCH MJ, et al: Detection of remote myocardial infarction in patients with positron emission transaxial tomography and intravenous ^{11}C-palmitate. *Circulation* 55:853-857, 1977
33. DUDCZAK R, SCHMOLINER R, DERFLER DK, et al: Effect of ischemia and pharmacological interventions on the myocardial elimination of I-123 heptadecanoic acid (HDA). *J Nucl Med* 23:P34, 1982 (abst)