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Gated Blood Pool Scintigraphic Monitoring of Doxorubicin Cardiomyopathy: Comparison of Camera and Computerized Probe Results in 101 Patients

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Serial gated blood pool scintigraphic monitoring of cardiac function with both a nonimaging scintillation probe and a conventional gamma camera-computer imaging system was performed in 101 patients receiving doxorubicin hydrochloride (Adriamycin) chemotherapy. Comparision of probe- and camera-derived ejection fractions (n = 287) correlated significantly (r = 0.70, p < 0.005) as did the interstudy (n = 183) change in ejection fraction (r = 0.76, p > 0.005). Significant discordance in probe- and camera-derived ejection fraction change occurred in 3 (1.6%) of 183 interstudy intervals. Average intrastudy variability of absolute probe-derived ejection fraction was 2.9%. This variability was unrelated to the level of cardiac function.

Thirteen patients (13%) developed clinical cardiotoxicity, including four at cumulative Adriamycin levels less than 450 mg/m^2. Mean absolute camera ejection fraction decline for these patients was 21% from baseline evaluation, and mean absolute probe ejection fraction decline was 22%. The minimal absolute ejection fraction decline was 11% for patients with clinical congestive heart failure. Eight asymptomatic patients had therapy terminated before the development of clinical cardiotoxicity after a mean decline in absolute camera ejection fraction of 19 ± 4% (SD) and in probe ejection fraction of 19 ± 9% into abnormal ranges (a decline in magnitude equivalent to that in patients developing congestive failure). None of these five asymptomatic patients available for clinical follow-up at 6 months after termination of Adriamycin therapy subsequently developed signs of ventricular dysfunction. The majority of patients (83%) studied at 450 mg/m^2 cumulative dose levels did not have a 15% or greater decline from baseline into the abnormal range.

Thus, variability of a probe-derived ejection fraction measurement was similar to that derived from a conventional camera system and was within acceptable limits for characterization of clinical Adriamycin cardiotoxicity. The probe provides a less expensive alternative method for monitoring of Adriamycin toxicity with similar reliability to the more elaborate camera-computer system.

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The anthracycline antibiotics are important antitumor agents currently used for the treatment of leukemias, lymphomas and numerous solid tumors. A clinical syndrome of severe and therapeutically refractory cardiomyopathy is a side effect of doxorubicin hydrochloride (Adriamycin) administration. The occurrence of the cardiomyopathy restricts the maximal tumoricidal potential of this most frequently administered anthracycline agent (1–3). The incidence of chronic doxorubicin toxicity has been controlled by limiting cumulative doses of Adriamycin to no more than 450 to 550 mg/m^2 because clinical manifestations of cardiomyopathy are infrequent below these levels (3,4). Serial determinations of left ventricular ejection fraction at rest by radionuclide imaging techniques utilizing single and multicrystal gamma camera-computer systems have effectively characterized dose-related myocardial depressive effects of chronic Adriamycin chemotherapy (5,6). On the basis of analysis of changes in ejection fraction, Alexander et al. (5) suggested that radionuclide monitoring of cardiac function during Adriamycin chemotherapy could predict the clinical onset of cardiotoxicity before clinical manifestations, thereby

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avoiding subsequent development of congestive heart failure. These determinations have allowed continued therapeutic benefits extending beyond relative empiric dose ceilings in the majority of patients.

Because of the increasing number of patients exposed to doxorubicin and related compounds and the expense associated with gamma camera-computer derived gated blood pool analysis, serial monitoring is potentially limited. An electrocardiogram-gated computerized scintillation probe (Nuclear Stethoscope, BIOS) provides a relatively inexpensive means of evaluating left ventricular function (7). Validation studies by several investigators (7–11) have demonstrated acceptable intraoperator and interoperator reproducibility of ejection fraction measurements with the hand-directed, microprocessor-guided probe. This report compares findings of conventional gated blood pool monitoring with probe data obtained in 101 patients receiving doxorubicin chemotherapy over an 18 month period.

Methods

Nuclear stethoscope cardiac probe. The hardware package consists of a 2 inch (5.08 cm) diameter × 1.5 inch (3.81 cm) deep sodium iodide crystal detector with a converging collimator designed to provide a 2.75 inch (6.99 cm) field of view at 1.5 inches (3.81 cm) from the collimator face. A dedicated microprocessor contains memory from which data are collected, and then displayed on a cathode-ray tube screen virtually instantaneously. The sensitivity of the system exceeds usual counting rates of 60 to 70 kilocounts. The probe energy detection window is preset for technetium with 20% acceptance around a 140 keV center line.

An algorithm has been incorporated into the microprocessor system to assist in positioning (8). The algorithm utilizes stroke volume, end-diastolic channel counts and synchrony with the electrocardiogram gating signal to identify optimal left ventricular and background sampling sites. After the administered blood pool dose has reached equilibrium, the probe is moved over the precordium in a raster-like pattern until these algorithms have been maximally fulfilled. Additional necessary variations in probe orientation are determined by the left ventricular positioning algorithm in approximately 10% of patients. This additional fine positioning of the probe presumably compensates for anatomic variations of body habitus and cardiac rotation.

Equilibrium blood pool mode monitoring of left ventricular activity was obtained in both beat to beat mode and the gated ventricular function mode. The higher temporal resolution gated ventricular function mode (10 ms/data point) was selected over the lower temporal resolution beat to beat mode (50 ms/data point) for data acquisition and clinical analysis. Data acquisition requires 30 to 60 seconds of sampling in the usual patient after labeling with an imaging dose of 20 mCi technetium blood pool agent. By operator placement of cursors on the time-activity curve display, the microprocessor derives the ejection fraction. The entire process of probe positioning, acquisition and data determination was obtained within 10 minutes in each patient studied.

Gated blood pool scintigraphy. Gated blood pool camera acquisitions were obtained with a standard gamma camera equipped with a general purpose low energy collimator. Data collection and processing were performed with a commercial minicomputer (MDS-A^2). Sixteen frame gated acquisitions were obtained with a count density of 300,000 counts in the end-diastolic frame using a standard field of view camera, and 500,000 counts with a large-field detector. Acquisitions were obtained in anterior and "best septal" left anterior oblique views. Quantitation of ejection fraction was derived from the left anterior oblique acquisition utilizing a semiautomated left venticular edge detection with variable region of interest method and a fixed region of interest paraventricular background determination method. Peak end-diastolic and end-systolic frames were automatically assigned for purposes of background correction and ejection fraction analysis (MDS-A^2 software).

Patient selection. The study group included 101 patients (18 men and 83 women) with various tumor diagnoses studied over an 18 month period; their mean age was 51 years (range 13 to 81). Interstudy time intervals were variable (mean 87 days; range 5 to 400) and determined clinically by the primary physician. A total of 287 probe-camera acquisitions were obtained (2 to 6 paired studies per patient). Chemotherapy was discontinued when there was significant clinical or radionuclide evidence of cardiotoxicity. Clinical criteria included the presence of a third heart sound, basilar rales, pleural effusion and other signs of congestive heart failure. Radionuclide criteria included an absolute decrease of 15% or greater in left ventricular ejection fraction into the abnormal range for camera ejection fraction ($\leq$55%) and probe ejection fraction ($\leq$58%) (5). In addition, patients with electrocardiographic signs of myocardial infarction were not included in the data analysis.

Protocol. Probe data were acquired by a single experienced operator after injection into the patient of 20 mCi technetium-99m blood pool agent (human serum albumin initially, later replaced by in vivo labeled red blood cells). Gated mode ventricular function probe data were compared with gamma camera ejection fraction data that were independently obtained and processed. Probe and camera comparison studies were performed in random sequence within the same hour. All studies were performed at least 48 hours after the previous administration of Adriamycin with a mean study time of 29 ± 12 (SD) days after the prior Adriamycin dose. Intraobserver variability of probe data was determined in 15 patients selected at random by performing an initial probe placement and acquisition, followed by the camera acquisition and finally followed by a repeat probe placement

JACC Vol. 8, No. 5
November 1986:1082–7

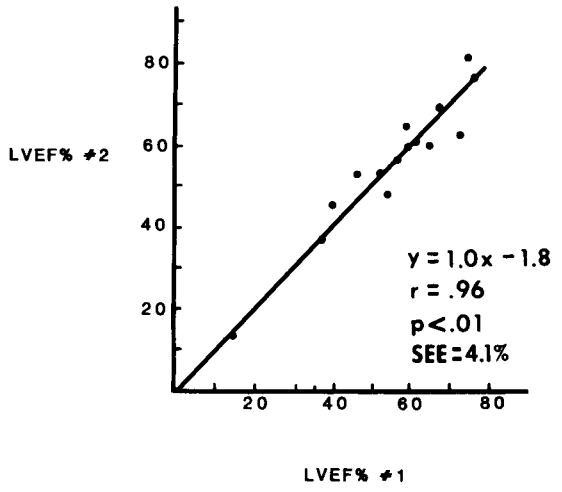


Figure 1. Linear regression analysis of intrastudy (n = 15) variation in probe-derived left ventricular ejection fraction (LVEF). Patients were restudied after repositioning of an algorithm-guided probe at least 30 minutes after the initial acquisition.

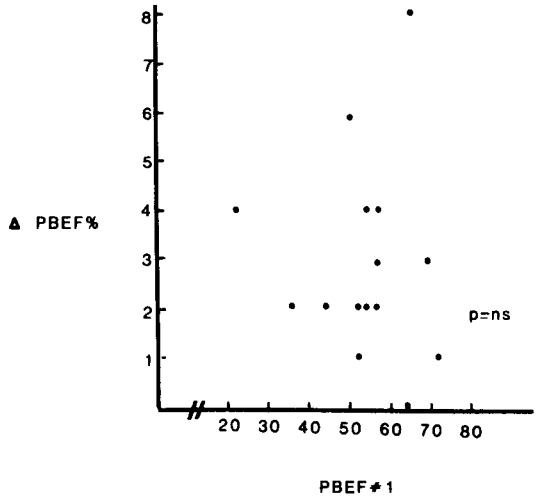


Figure 2. Regression analysis comparing the intrastudy variations in absolute probe-derived left ventricular ejection fraction (Δ PBEF%) with the level of ventricular performance expressed as the initial ejection fraction (PBEF #1). Intrastudy variation is unrelated to the level of cardiac function. ns = not significant.

and acquisition approximately 30 minutes later. All acquisitions and processing were performed by different operators without knowledge of prior quantitative results, cumulative Adriamycin dose received or clinical data.

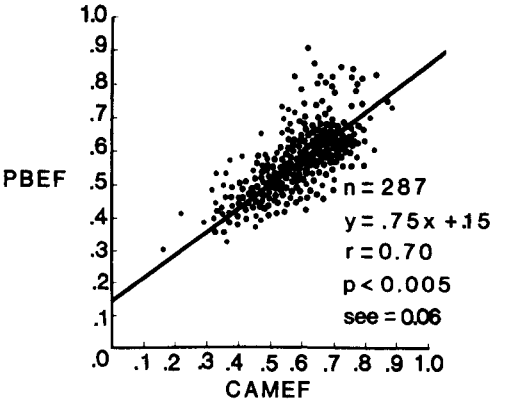
Statistical analysis. Inference of significance was derived from a Student distribution with two tails. Intrastudy variability of probe-derived variables was determined by root mean square determination of standard deviation from repeated acquisition. A similar method previously utilized in our laboratory determined the variability of camera-derived absolute ejection fraction at rest to be ± 3% (SD).

Results

Reproducibility of probe-derived ejection fraction. In the 15 patients who were studied twice, the average change between the two studies was 2.9% (4.1%, SEE) for absolute left ventricular ejection fraction (Fig. 1.) Standard deviation determination by root mean square analysis revealed that the intrastudy variability was 3.4% for ejection fraction. Linear regression analysis revealed no significant correlation betwen the extent of variability of ejection fraction and cardiac function (Fig. 2).

Serial monitoring data. Left ventricular ejection fraction at rest determined from the camera and the probe were compared in 101 patients undergoing 287 paired evaluations. Individual probe data correlated with gated blood pool studies ($r = 0.70$, $p > 0.005$) (Fig. 3). Correlation of the interstudy change in ejection fraction as determined both with the camera and the probe for 183 patient intervals was also highly significant ($r = 0.76$, $p > 0.005$) (Fig. 3). A concordant probe ejection fraction and camera ejection fraction change of significance from the previous study (defined as ±2 SD interval ejection fraction change) occurred in 103 (56%) of the 183 monitored intervals (Fig.4). Significant augmentation (≥6% improvement in both camera ejection fraction and probe ejection fraction) occurred in 27 (26%) of these 103 intervals. A significant decline (≥6% decline in camera ejection fraction and probe ejection fraction) occurred in 76 (74%) of the 103 intervals. Insignificant change (less than ±6% variation in both camera ejection fraction and probe ejection fraction) occurred in 58 intervals (32%). A discordant change in probe ejection fraction defined as a ±6% (2 SD) interval probe ejection fraction change without a parallel significant camera ejection fraction variation of ±6% (2 SD) occurred in 22 (12%) of the 183 intervals.

Figure 3. Linear regression analysis of gated blood pool ejection fraction analysis determined by the cardiac probe (PBEF) and a conventional camera computer system (CAMEF) reveals a highly significant correlation between the imaging and nonimaging data.



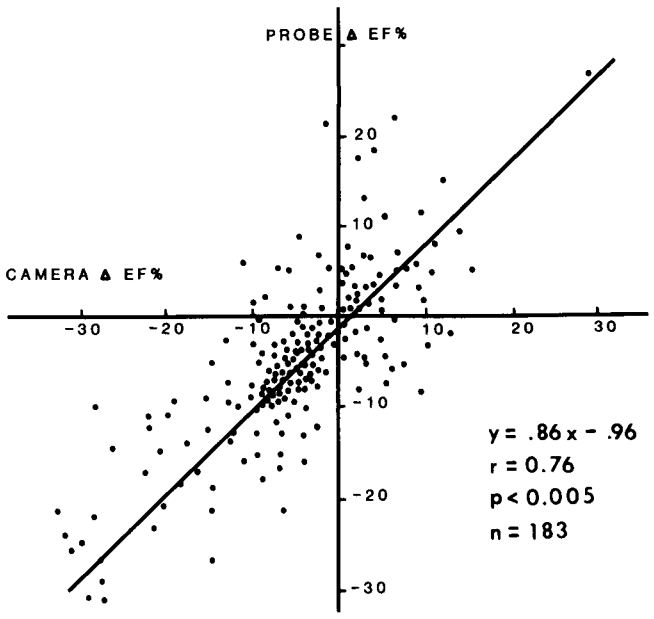


Figure 4. Linear regression analysis of interstudy patient data (183 study intervals) comparing inverval absolute change in camera-derived ejection fraction (camera Δ EF%) and cardiac probe-derived ejection fraction (probe Δ EF%) in patients receiving varying doses of adriamycin at widely varying time intervals (0 to 600 days).

Serious discordant changes (directionally opposite changes of ±2 SD of probe ejection fraction and camera ejection fraction, respectively) occurred in only three interstudy intervals (1.6%).

Aggregate ejection fraction data (n = 287) revealed no correlation between cumulative Adriamycin dose and absolute probe ejection fraction or camera ejection fraction (Fig. 5 and 6).

Clinical cardiotoxicity. Thirteen patients developed clinical signs of left ventricular dysfunction and failure during the period of Adriamycin therapy monitoring. At the first manifestation of left ventricular dysfunction, camera ejection fraction for these patients ranged from 29 to 47% (mean 37 ± 6%; normal camera ejection fraction is 55% or less). The range of absolute camera ejection fraction decline from baseline was 13 to 32% (mean 21 ± 9%). The range of absolute probe ejection fraction decline from baseline was 11 to 48% (mean 22 ± 11%). Four of the 13 patients developed clinical ventricular dysfunction at cumulative Adriamycin dose levels less than 450 mg/m^2 (320, 365, 400 and 425 mg/m^2). Mean camera ejection fraction for these four patients was 33 ± 3% (range 29 to 36%) at the time of premature development of left ventricular dysfunction; their average baseline camera ejection fraction (59%) was not significantly different than that of the nine patients (60%), developing congestive heart failure at cumulative doses in excess of 450 mg/m^2. In these nine patients, clinical factors necessitated continued Adriamycin therapy exceeding the empiric dose restrictions. These nine patients received a mean additional dose of 135 mg/m^2 (average total cumulative dose 585, range 520 to 710) before termination of therapy with a mean camera ejection fraction of 39% (range 29 to 47%).

Twenty-four (83%) of 29 patients studied at or beyond the empiric cumulative Adriamycin dose ceiling of 450 mg/m^2 did not develop signs of congestive failure or the cardiotoxicity criteria of Alexander et al.(5) of a 15% absolute decrease of left ventricular ejection fraction into the abnormal range. There were eight patients whose therapy was terminated before the development of signs of left ventricular dysfunction because of a 15% absolute left ventricular ejection fraction decline from baseline into the abnormal range for both camera ejection fraction and probe ejection fraction. Mean cumulative dose for this group was 558 ± 138 mg/m^2 (range 350 to 750). The five patients from this group who were available for clinical follow-up at 6 months

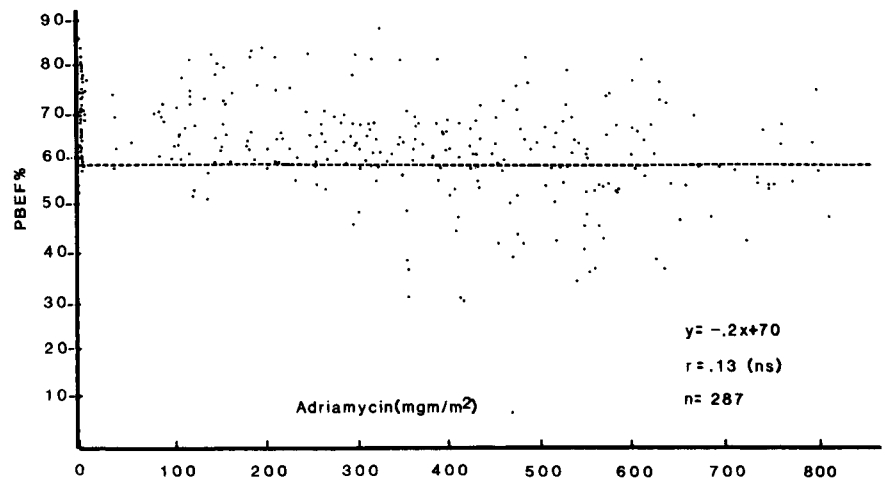


Figure 5. Comparison of probe-derived ejection fraction (PBEF%) and cumulative adriamycin dose reveals no direct correlation. Horizontal **dashed line** represents previously determined normal range for ejection fraction (≥58%) (8). ns = not significant.

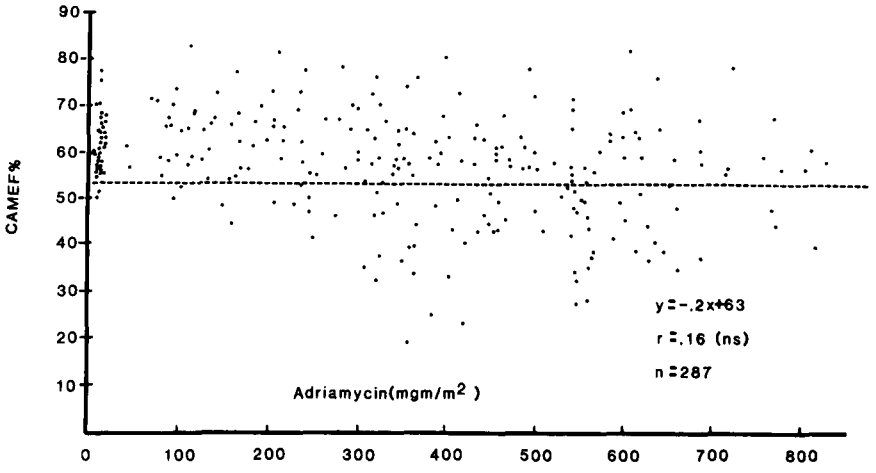


Figure 6. Camera-derived ejection fraction (CAMEF%) and cumulative adriamycin dose reveals no direct correlation. **Dashed line** signifies normal camera ejection fraction range (≥55%). ns = not significant.

after termination of Adriamycin therapy had not developed signs of left ventricular dysfunction. The mean baseline camera ejection fraction was 63 ± 5% (range 55 to 70) in these eight patients. There was no significant difference in baseline camera ejection fraction between the two groups fulfilling the radionuclide cardiotoxicity criteria of Alexander et al. (5), those without clinical failure and those developing clinical failure. There was no significant difference in amount of absolute decline in camera ejection fraction and probe ejection fraction from baseline in the two groups: mean decline in camera ejection fraction units without development of left ventricular failure was 18.7 ± 4.2 versus 20.5 ± 8.6 for those developing clinical left ventricular failure (p = NS). Mean decline in probe ejection fraction without development of clinical signs of congestive failure was 18.6 ± 8.9 versus 21.5 ± 10.6 for those developing failure (p = NS).

Discussion

The results of this study show that ejection fraction data derived from gated blood pool monitoring with the cardiac probe are reproducible and provide clinically useful data ordinarily obtained with the more elaborate gamma camera computer system. A clinically significant difference between probe ejection fraction and camera ejection fraction occurred in 3 (1.6%) of 183 study intervals. Assuming that the difference represented probe error, this difference was possibly due to failure of the positioning algorithm to accurately determine probe sampling sites for the left ventricle or background, or both. Another explanation would be failure of the operator to respond to the microprocessor optical cues for proper positioning. Finally inadvertent movement of the patient or the probe after accurate microprocessor-guided probe placement during subsequent data collection could have introduced error. Microprocessor-guided operator probe placement is a learned skill, providing a potential for error in data collection. Nonetheless, this error was rare, because 180 (98%) of 183 intervals were concordant within the confidence limits set by the variability of both system measurements of ejection fraction.

Clinical significance. Comparison of probe- and camera-derived ejection fraction data revealed that probe data proved as reliable as that from the camera in predicting cardiotoxicity: all patients developing clinical cardiotoxicity had an 11% or greater absolute left ventricular ejection fraction decline into the abnormal range as determined by both camera and probe. The radionuclide cardiotoxicity criteria of Alexander et al. (5) of a 15% or greater left ventricular ejection fraction decline into the abnormal range did characterize a small group of patients (n = 8) without clinical manifestations of cardiotoxicity who failed to develop subsequent clinical cardiotoxicity after discontinuation of additional doxorubicin treatments. The criterion was not specific for subclinical cardiotoxicity, because an equivalent decline in left ventricular ejection fraction from baseline also characterized those patients (n = 13) with clinically manifested cardiotoxicity. In these patients, more frequent radionuclide evaluation would have been necessary to better characterize subclinical involvement as well as to predict the critical additional dose of Adriamycin responsible for progression of cardiotoxicity from a subclinical to a clinical level. It is also possible that changes in loading conditions due to dehydration, hypertension or toxic states could either exaggerate or mask a significant decline in ejection fraction. The unexpected significant decline of left ventricular ejection fraction with attendant congestive heart failure in four patients at low cumulative Adriamycin doses (320, 365, 400 and 425 mg/m^2) further supports the need to reassess cardiac function at earlier and more frequent intermediate dose levels as well as at the empiric dose ceiling of 450 mg/m^2 and beyond. Only in this way would it be possible for patients with increased susceptibility to the cardiotoxic side effects

of Adriamycin to be distinguished at early treatment levels from the majority who safely tolerate significant additional Adriamycin therapy beyond arbitrary dose restrictions.

Limitations of the study. This report represents a retrospective analysis of data rather than a structured protocol with fixed follow-up intervals and indications for study. Patient referrals, therefore, were based on heterogeneous criteria individually determined by each referring physician. The most common referral indication was routine follow-up before the next scheduled administration of Adriamycin. However, a changing clinical status of the patient as an indication for study could introduce selection bias into the data base.

Accordingly, our failure to clearly distinguish subclinical from clinical cardiotoxicity with a criterion of measured ejection fraction change may be explained by both the patient referral pattern and the need for more frequent radionuclide assessment than was utilized in our study (mean number of assessments per patient = 2.85 studies, mean interval dose = 168 mg/m^2). A less likely explanation is a difference in precision of ejection fraction measurement, because the range of reproducibility of ejection fraction measurements of the multicrystal camera-monitored first pass technique of Alexander et al. (5) (± 4%) was essentially equivalent to the reproducibility of either our camera-derived ejection fraction (± 3%) or our probe-derived ejection fraction (± 3%).

Conclusions. Because of the large number of patients receiving Adriamycin and the demonstrated necessity to frequently evaluate dose-related changes in cardiac function to account for the apparent wide biologic variation in dose-related cardiotoxicity, utilization of a small, portable and relatively inexpensive nuclear cardiac probe offers the potential for more comprehensive application of gated blood pool monitoring. The nonimaging computerized probe appears to be an acceptable alternative to a more elaborate and costly imaging system for monitoring the development of subclinical doxorubicin cardiotoxicity. This study shows that ejection fraction data derived from the Nuclear Stethoscope cardiac probe proved as reliable as those from the camera in determining cardiotoxicity. Probe portability and speed of data recovery could more easily accommodate future studies by providing immediate ejection fraction data at the site of chemotherapy in the oncology clinic or at the bedside.

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