Diminishment of Respiratory Sinus Arrhythmia Foreshadows Doxorubicin-Induced Cardiomyopathy

William J.M. Hrushesky, MD; Darrell J. Fader, BS; John S. Berestka, MD; Marc Sommer, MS; James Hayes, PhD; and Frederick O. Cope, PhD

Background. The development of a microcomputer-based device permits quick, simple, and noninvasive quantification of the respiratory sinus arrhythmia (RSA) during quiet breathing.

Methods and Results. We prospectively and serially measured the radionuclide left ventricular ejection fraction and the RSA amplitude in 34 cancer patients receiving up to nine monthly bolus treatments with doxorubicin hydrochloride (60 mg/m²). Of the eight patients who ultimately developed symptomatic doxorubicin-induced congestive heart failure, seven (87.5%) demonstrated a significant decline in RSA amplitude; five of 26 subjects without clinical symptoms of cardiotoxicity (19.2%) showed a similar RSA amplitude decline. On average, significant RSA amplitude decline occurred 3 months before the last planned doxorubicin dose in patients destined to develop clinical congestive heart failure.

Conclusion. Overall, RSA amplitude abnormality proved to be a more specific predictor of clinically significant congestive heart failure than did serial resting radionuclide ejection fractions. (Circulation 1991;84:697–707)

Doxorubicin hydrochloride is one of the most frequently used and broadly active chemotherapeutic agents available for the treatment of common cancers, having been administered to more than five million cancer patients in the United States alone. Unfortunately, the prolonged survival of successfully treated cancer patients has revealed delayed cardiotoxicity to be a major and dose-limiting side effect of doxorubicin therapy. This toxicity, or fear of inducing it, often limits the total amount of doxorubicin given, even when the drug is primarily responsible for control or potential cure of the patient’s cancer. When cumulative doses of intermittent bolus doxorubicin exceed 550 mg/m², doxorubicin-induced cardiac failure occurs in 5–10% of patients; of this number, one fourth succumb to the syndrome, one half require lifelong cardiac treatment, and one fourth recover satisfactorily. Anti-cancer drug dose intensity can be a critical factor in determining whether patients will respond to chemotherapy, how well their cancers will be controlled, and whether they will be cured. Because concern for delayed congestive heart failure (CHF) very frequently limits the dose intensity of doxorubicin therapy, oncologists are continuously faced with the difficult task of determining when it is safe for a patient to receive further doxorubicin therapy without undue risk of major delayed cardiac dysfunction. This risk–benefit assessment could benefit from a simple, reliable, noninvasive test with some predictive value.

The respiratory sinus arrhythmia (RSA) is a physiological phenomenon that diminishes predictably with advancing age (Figure 1). This observation suggested to us that quantitatively assessed RSA might provide a reliable measure of myocardial health and function and that changes in this physiological phenomenon might reliably predict the development of clinically significant doxorubicin cardiotoxicity. This paper describes the effect of doxorubicin administration on the amount of rhythmic heart rate change during normal breathing (RSA amplitude). Serial RSA amplitude quantification (expressed as percentage expected for age) is compared...
FIGURE 1. Age-related decline in amplitude of respiratory sinus arrhythmia (RSA) observed in 326 clinically healthy individuals ranging from 7 to 80 years of age. Points represent mean±SEM for n=11, 5-year subgroups. On average, the amplitude of the RSA declines 10% per decade between the second and ninth decades of life.

Materials and Methods

Intertest Variability

Twenty-five presumably healthy individuals aged 20 to 82 years, taking no medications, were tested serially before and after venipuncture, in the morning of the same day at 7 AM and 9 AM, respectively. Intraindividual and intertest variabilities were then quantified and contrasted by two-way analysis of variance. The heart rate, amplitude, and phasing of the RSA showed relative stability. The degree of intraindividual variability in these parameters was always much smaller than the amount of interindividual variability (Table 1). In this and other populations similarly studied, the mean heart rate, amplitude, and phasing of the RSA showed relative intraindividual intertest stability. The amount of heart rate and RSA amplitude variability due to age class or between individuals was always far

<table>
<thead>
<tr>
<th>Time of testing</th>
<th>Subjects (n)</th>
<th>Mean (beats/min)</th>
<th>Amplitude (beats/min)</th>
<th>Timing of peak rate, beats (1–5)</th>
<th>5-Beat rhythm (p)</th>
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<tbody>
<tr>
<td>Absolute data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 AM</td>
<td>25</td>
<td>73.97 (69.90,78.02)</td>
<td>2.12 (1.56,2.68)</td>
<td>2.00 (1.80,2.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9 AM</td>
<td>25</td>
<td>72.49 (68.15,76.81)</td>
<td>2.34 (1.74,2.94)</td>
<td>1.86 (1.74,1.95)</td>
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<tr>
<td>F test, df (1,48)</td>
<td></td>
<td>0.26</td>
<td>0.32</td>
<td>1.87</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.61</td>
<td>0.57</td>
<td>0.18</td>
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Data expressed as percent of mean

<table>
<thead>
<tr>
<th>Time of testing</th>
<th>Subjects (n)</th>
<th>Mean (beats/min)</th>
<th>Amplitude (beats/min)</th>
<th>Timing of peak rate, beats (1–5)</th>
<th>5-Beat rhythm (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 AM</td>
<td>25</td>
<td>100.0 (98.5,102.3)</td>
<td>3.0 (2.2,3.8)</td>
<td>1.97 (1.78,2.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9 AM</td>
<td>25</td>
<td>98.7 (96.6,100.8)</td>
<td>3.2 (2.4,4.0)</td>
<td>1.84 (1.72,1.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>F test, df (1,48)</td>
<td></td>
<td>1.54</td>
<td>0.20</td>
<td>1.66</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.22</td>
<td>0.65</td>
<td>0.20</td>
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</tbody>
</table>

Values in parentheses are 95% confidence intervals. Although two-way analysis of variance by time and beat corroborated the significant effect of beat (p of five-beat rhythm), there was no significant effect of time of testing (F test; p value for 7 AM vs. 9 AM) on the five-beat sinus arrhythmia. Rhythm characteristics (amplitude and peak pulse phase) tested in all combinations showed no significant differences for 7 AM or 9 AM.
greater than that secondary to (intraindividual) test-to-test differences.12

**Patients**

The cumulative effects of doxorubicin were evaluated in 34 cancer patients, each of whom was scheduled to receive 540 mg/m² doxorubicin in courses of 60 mg/m² per month as an intravenous bolus over a span of 9 months. We endeavored to measure patients’ RSA prior to the first, fifth, and ninth doxorubicin courses of their treatment. Only patients with adequate numbers of either serial RSA or radionuclide ejection fraction measurements were judged adequately assessable. No individual who developed CHF had fewer than two measurements of both end points. Behavior of the RSA amplitude was not known to clinicians caring for patients; therefore, abnormalities of RSA amplitude did not affect decisions about doxorubicin therapy. Ejection fraction determinations were, however, routinely reported to the physicians caring for these cancer patients. Because patients with abnormal ejection fraction test results were more likely to receive follow-up ejection fraction determination, patients with abnormal ejection fractions were therefore more likely to be assessable. Because of this selection, it is not possible to draw firm conclusions about the overall frequency of CHF in this population of patients. The comparison of the relative utility of these two tests was, however, unaffected by this selection. Each patient was followed for at least 2 years after the final doxorubicin dose or until death. No patient was lost to follow-up.

Twenty-four women and 10 men, aged 19–78 years, with either advanced ovarian or bladder cancer, were studied (Table 2). Monthly doxorubicin (60 mg/m²) was infused first over 30 minutes, followed by 60 mg/m² i.v. bolus cisplatin 12 hours later. Measurements of RSA were taken approximately 30 minutes before that month’s doxorubicin was administered. No patient had received any chemotherapy for at least 28 days before each RSA measurement and/or ejection fraction determination. No antiemetics, sedatives, or other drugs were administered before doxorubicin. Table 2 summarizes cardiac findings in the 34 patients during a median of nine monthly doxorubicin treatments (60 mg/m²) and follow-up of 2 years or until death from cancer. No patient died of heart failure.

**Symptoms**

Symptoms of CHF were classed according to the definition of the New York Heart Association: Class I, dyspnea upon maximal exertion; Class II, dyspnea upon moderate effort; Class III, dyspnea upon minimal effort; Class IV, dyspnea at rest. Seven of eight individuals who were judged to have doxorubicin-induced heart failure had dyspnea at rest or with minimal effort, and each complained of profound fatigue; the remaining patients had dyspnea with moderate effort. Three of the 26 patients who received doxorubicin but were not judged overall to be suffering from significant doxorubicin-induced heart damage complained of dyspnea upon maximal exertion at some time during either treatment or follow-up. New paroxysmal nocturnal dyspnea was noted by five of eight of the patients judged to have doxorubicin-induced heart failure. At presentation, significant new pedal edema was present in five of eight of these patients and in none of the other 26 patients.

**Signs**

Signs of CHF, including a new S₃ gallop, new rales, and new elevation of the internal jugular venous pressure, were limited to the group of patients judged to have doxorubicin cardiotoxicity. At presentation, significant new pedal edema was present in five of eight of these patients and in none of the other 26 patients.

**Chest X-ray**

Radiographic findings including increased heart size (greater than 20%) from baseline occurred in each of the eight who developed CHF and in three of the 26 patients who did not develop the full-blown clinical syndrome. New or significantly increased cephalization occurred in each of the eight and none of the 26 patients in each clinical group, whereas new nonmalig-
TABLE 3. Patient Characteristics of Groups With and Without Clinical Doxorubicin-Induced Congestive Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>CHF</th>
<th>Asymptomatic</th>
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<tbody>
<tr>
<td>Patients (n)</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>19–71</td>
<td>24–78</td>
</tr>
<tr>
<td>Median</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>56±6</td>
<td>60±3</td>
</tr>
<tr>
<td>Cumulative doxorubicin dose (mg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>540–550</td>
<td>300–550</td>
</tr>
<tr>
<td>Median</td>
<td>540</td>
<td>510</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>541±1</td>
<td>485±19</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure.

nent pleural effusion occurred only in three of eight of the patients judged to be suffering from significant doxorubicin-induced cardiac damage. It should be noted that these three patients were not necessarily the same as those three individuals who complained of shortness of breath upon maximal exertion.

Electrocardiography

Diminished (from baseline) QRS voltage on electrocardiogram, thought to suggest the syndrome, was present in the minority of patients who had the clinical syndrome (three of eight) but in none of the 26 individuals in the other group.

Gender

The ratio imbalance in the number of men and women who develop CHF, obvious in Table 3, is at least in part explained by the sex dependence of tumor type and, therefore, outcome in these patients. Ovarian cancer is more successfully treated with chemotherapy than is transitional-cell bladder cancer, whereas bladder cancer is predominantly a disease of older men. In fact, 80% of the bladder cancer patients in this series are male and because these individuals more frequently failed therapy, they sometimes received somewhat lower cumulative doxorubicin doses. Men received a mean of 474±31 mg/m², whereas women received an average of 516±15 mg/m² (not statistically different at the 5% level). Therefore, by virtue of diagnosis and average doxorubicin exposure, males were at lower risk for the development of doxorubicin-induced CHF. No single-sex predominance has been reported for doxorubicin-induced CHF to date. The confounding aspect of sex-dependent diagnosis and doxorubicin dose allows no such conclusion to be drawn from our data.

Definition of Clinical Doxorubicin-Induced CHF

Doxorubicin-induced CHF was determined by the presence of the classic syndrome of relatively sudden onset of new CHF in the absence of other causes and was confirmed by symptom history and physical find-ings, as well as chest radiography and electrocardiography and/or cardiac enzyme determinations to exclude acute myocardial infarction. Additional non-invasive (echo and Doppler) and invasive studies, including Swan-Ganz catheter placement and pressure recordings, were obtained if there was any clinical doubt about the diagnosis. All ejection fractions and RSA amplitude measurements were made at least 28 days from chemotherapy administration, at a time of low risk for leukopenia and anemia. No measurements were made in the presence of active infection or severe anemia. Patients who required transfusion were always transfused at least 7 days before measurement of ejection fraction or RSA amplitude.

Serial Neurological Evaluation

Patients in this study underwent careful serial neurological examination by a staff neurologist before the beginning of treatment and after the fifth and ninth treatments. These evaluations demonstrated several interesting findings, including a predictable sensory neuropathy known to result from cisplatin. Serial neurological evaluations revealed that no patient developed any symptom, sign, or physical finding compatible with autonomic neuropathy.

Quantification of the RSA

All RSA measurements were made using a computer-based pulse monitor during voluntary cardiorespiratory synchronization. The principal features of this device and the method for its use have been summarized elsewhere. Briefly, the pulse monitor measures the relation of respiration and heart rate by collecting instantaneous heart-rate data through a noninvasive earclip (as calculated from the pulse–pulse intervals) while simultaneously measuring inhalation and exhalation with a thermal sensor in a respiratory mouthpiece. Symbols on a computer screen tell the subject when to inhale and exhale, thereby synchronizing the subject’s cardiac and respiratory cycles so that an inhalation occurs during two heartbeats and an exhalation during three heartbeats. Respiratory volume is fixed at the patient’s usual tidal volume. The software then fits the instantaneous heart rates to the best-fitting cosine curve by least-squares analysis with a period length equal to the respiratory cycle, each of which comprises six measured pulses. The amplitude (one half the peak–trough difference) of this modeled curve is the datum used to quantify the RSA of each subject.

All data in this report were obtained using the ratio of two beats for inspiration followed by three beats for expiration, but any desired ratio may be studied in this way. The beat-to-beat interval translated to instantaneous heart rate is the experimental datum. These data were sorted and stored according to their exact position in the five-beat cycle and then analyzed. The first pulse corresponds to the interval between the first and second beats of the inspiration phase of the respiratory cycle.
Biological functions are rhythmic within many time frames. The RSA represents an ultradian or high-frequency biological rhythm. All data are analyzed and reported independent of time in terms of the arbitrarily preselected and standardized period length of five heartbeats. The data are expressed as average instantaneous heart rate during each of the five beats of this five-beat rhythm. If the average pulse during 1 minute is 75 beats/min, 15 continuous pulse cycles of a five-beat rhythm are evaluated in that minute. Single cosinor analysis was used to investigate each series of pulse data for five-beat rhythmicity. This analysis involves a least-squares regression fit of a cosine curve to the data points. The fitted curve describes the shape of this rhythm by providing the mean pulse rate, the amplitude, and the timing of the peak with their respective 95% confidence intervals. The population mean cosinor analysis was used to investigate whether the rhythm characteristics of individual data series were consistent.

Heart-rate data were collected for at least 10 respiratory cycles per test (about 1 minute), with two tests obtained for each subject at each testing session. Classic analyses of variance were used in addition to cosinor analysis to discern individual and group differences in mean RSA amplitude. A statistically significant rhythm is described by 1) a good least-squares curve fit that successfully rejects the zero-amplitude hypothesis \( p < 0.05 \) and 2) pulse mean differences throughout the respiratory cycle (beats 1–6; analysis of variance with \( p < 0.05 \)). If the patient fell out of cardiorespiratory synchronization before the end of the test, these cycles were automatically eliminated, and the data for a smaller number of cycles were included. If fewer than three respiratory cycles (18 heartbeats) showed adequate synchronization, the data for that test were excluded from the study. All data were filtered to remove any ectopic beats. An R-R interval greater than 2 SDs of the mean caused automatic elimination of that cycle from analysis. Voluntary cardiorespiratory synchronization was initially required during testing in order to internally standardize breathing pattern with pulse and decrease interindividual variability in respiratory pattern during testing. Subsequent software modifications of the pulse monitor have made this voluntary maneuver optional. Subsequently, a careful study of a large group of individuals during both voluntary cardiorespiratory synchronization and “natural” breathing reveals no statistically significant differences between their RSAs, regardless of whether the voluntary synchronization procedure is employed.

All data in this paper were collected using the synchronized technique.

A total of 42 RSA measurement sessions were obtained from the eight patients who developed clinical CHF (an average of 5.25 serial measurements per subject), whereas 169 tests were recorded from the 26 asymptomatic individuals (an average of 6.5 serial measurements per subject).

**Amplitude Normalization**

RSA amplitudes were expressed as a percentage of the amplitude expected for age (observed divided by the amplitude expected for age and multiplied by 100). The amplitudes expected for age were generated from a regression analysis of data collected from 326 healthy males and females 7–80 years of age with no history of cardiovascular or pulmonary disease and taking no cardiac medication. In this group of controls, the average RSA for the youngest subjects (\( n = 17 \), age range 7–15 years) was greater than 8 beats/min and decreased approximately 10% per decade so that the oldest subjects (\( n = 11 \), age range 76–80 years) had a mean RSA of less than 2 beats/min. The equation used to determine age-expected amplitude was \( Y = -0.1014X + 8.6021 \), where \( X \) is age in years and \( Y \) is amplitude (beats per minute). A decline in RSA amplitude below one half that expected for age was considered a positive test result indicative of a high likelihood of cardiotoxicity. Figure 1 demonstrates the predictable relation of age to RSA amplitude.

**Radionuclide Ventriculography**

Red blood cells were labeled using the modified in vivo labeling technique of Callahan et al. The protocol was modified in that 0.5 cc adenine citrate dextrose solution rather than heparin was used. Briefly, patients received approximately 500 \( \mu \)g of stannous ion as stannous pyrophosphate intravenously. Twenty minutes later a butterfly infusion set was placed in an antecubital vein. Three ml blood was withdrawn into a shielded syringe containing 20 mCi technetium-99m pertechnetate and 0.5 cc adenine citrate dextrose (ACD). The intravenous line was anticoagulated with 10 units/ml heparin. After 5 minutes of incubation with gentle agitation at room temperature, the labeled red blood cells were reinjected.

Imaging was conducted using a large field-of-view gamma camera equipped with a computer (GE Star) and an electrocardiographic synchronizer. A 45° left anterior oblique view with 10° caudal angulation, as well as anterior view, was acquired. Data were acquired for 10 minutes or until 250,000 counts/frame were acquired. The 24 frames were then smoothed temporally and spatially. Left ventricular end-diastolic and end-systolic counts were determined from the background-subtracted left ventricular time–activity curve. The ejection fraction was calculated from the relation

\[
EF = \frac{C_D - C_S}{C_D}
\]

where EF is ejection fraction, \( C_D \) is counts at end diastole, and \( C_S \) is counts at end systole. The study was visually assessed by a nuclear medicine physician to ensure that the edge of the ventricle was accurately detected, that the background region of interest was appropriately placed, that the patient was adequately positioned, that electrocardiographic gat-
ing was successful, and that wall motion was evaluated for focal abnormalities.

Left ventricular ejection fractions were obtained directly from the nuclear medicine films in each subject's hospital file. Ejection fraction data were expressed in two ways: 1) as an absolute ejection fraction and 2) as a percentage of initial ejection fraction (taken before the onset of doxorubicin treatment). A positive result for cardiotoxicity was considered by five routine cutoff techniques: ejection fraction of less than 55%, less than 50%, or less than 45%; or a fall in ejection fraction of 10% or greater or 15% or greater. The University of Minnesota Hospital's Nuclear Medicine Division routinely considers a fall of 5% or greater as being a significant decline and an ejection fraction value of less than 50% as being abnormal. In addition to these numerical values, a subjective assessment of the quality of ventricular wall motion was also reported.

Radionuclide ventriculography was routinely performed before the first, fifth, and ninth treatments. Additional tests were also obtained at later stages of doxorubicin treatment when clinically indicated. Adequate data (at least three serial studies) for three asymptomatic subjects were not available, however, so these individuals (who did have serial RSA determinations) are not included for the evaluation of ejection fraction. A total of 70 ejection fractions were recorded for individuals who did not develop significant CHF (an average of 3.0 serial measurements per subject, n=23), whereas 31 such tests were done in patients who ultimately developed significant CHF (an average of 3.9 serial measurements per subject, n=8).

**Results**

**Effects of Doxorubicin on the RSA Amplitude**

Table 3 shows that eight subjects developed classic symptomatic doxorubicin-induced CHF, whereas 26 individuals had no cardiac problems during treatment or follow-up spans. Seven of the eight individuals who later suffered symptomatic doxorubicin-induced CHF also had falls in RSA amplitude to or below 50% of that expected for age. Five of the 26 asymptomatic patients (19.2%) also had falls in RSA to or below 50% of the value expected for age. During the 9 months of therapy, no predictable decline in RSA amplitude was observed in the group of patients who later proved to be free of significant CHF after adequate follow-up (amplitude as percent expected for age versus doxorubicin course number: r=-0.02, p=NS). The RSA amplitude of those who developed CHF, however, fell with increasing dosage, an average of 4.1% per course (amplitude as percent expected for age versus doxorubicin course number: r=-0.41, p<0.008). Similarly, analyses of variance confirmed this correlation by demonstrating a significant mean fall of RSA amplitude in the CHF group (F=2.783, p<0.03) yet no mean decrease of RSA amplitude was uncovered in the asymptomatic group (F=0.798, p>0.60, Figure 2). Figure 2 also demonstrates that the decline in amplitude in the heart-damaged group was premonitory, occurring several months before the diagnosis of clinical doxorubicin-induced CHF could be made and, more importantly, several months before the last planned monthly doxorubicin dose.

**Behavior of Resting Left Ventricular Ejection Fraction During Doxorubicin Administration**

Because of the considerable argument in the literature as to what constitutes a significantly abnormal test result for cardiotoxicity, five separate cutoff points were used to evaluate what might indicate a significantly abnormal test result. The resulting sensitivity and specificity figures for each method are depicted in Table 4. For example, when an ejection
fraction below 50% was considered predictive of or suspicious for CHF, five of the eight symptomatic patients were detected. Only four of the eight had ejection fractions below 45% or showed a net decline of more than 10% throughout therapy. In addition, Table 4 shows that regardless of commonly chosen cutoff points for ejection fraction results, RSA amplitude proved comparatively more capable of discerning those individuals with drug-induced CHF from those without.

The behavior of the mean value of the ejection fraction was also analyzed by two-way analysis of variance techniques as a function of the doxorubicin course number and revealed no difference between the heart-damaged and asymptomatic groups, with mean values of both groups falling similarly (see Figure 3). Linear regression analyses of the behavior of absolute ejection fraction over time (doxorubicin course) clearly demonstrate longitudinal declines with very similar slopes in both groups (clinically significant cardiotoxicity: \( r = -0.39, p < 0.04 \), slope of 1.7% per course; no clinical cardiotoxicity: \( r = -0.51, p < 0.001 \), slope of 1.8% per course). A similar effect of treatment is seen when ejection fraction is expressed as a percentage of the initial ejection fraction (clinically significant cardiotoxicity: \( r = -0.41, p < 0.05 \), slope of 2.6% per course; no clinical cardiotoxicity: \( r = -0.52, p < 0.001 \), slope of 2.9% per course).

Interpretation of the above description of the longitudinal behavior of the RSA and the ventricular ejection fraction of groups of eight and 26 cancer patients who ultimately did or did not develop doxorubicin-induced congestive cardiomyopathy, respectively, must be qualified by the fact that the analyses of prospectively obtained data have been performed retrospectively. The strength of this approach ensured that changes in the RSA did not affect how the patients were treated. The disadvantage of this approach is that because the data were not being used for clinical decision making, the test was not performed as frequently as might have been optimal. Interindividual variability of the test in health has been shown to be minimal; in disease, however, less is known. Although behavior of the group data indicates that RSA falloff may be premonitory, this conclusion cannot be drawn without denser individual prospective longitudinal data to further gauge the variability of individual RSA and ejection fraction. Figures 4 and 5 indicate the individual behavior of RSA and ejection fraction in each of the eight patients who ultimately developed CHF.

**Discussion**

Although doxorubicin is most commonly associated with clinically significant cardiotoxicity, this tox-
FIGURE 3. Chronic effects of doxorubicin on ejection fraction in cancer patients with (n=8, closed circles) and without (n=23, open circles) clinical doxorubicin-induced congestive heart failure (CHF). Whether ejection fraction is expressed absolutely (not shown) or as a percentage of the initial pretreatment value, as in the figure, there is no longitudinal difference between the two very different clinical groups. Analysis of variance quantifying progressive mean fall-off of the ejection fraction is statistically significant only for the values from the group that did not develop the clinical syndrome of doxorubicin-induced CHF (asymptomatic: F=4.35, p<0.01; CHF: F=1.95, p>0.10). Linear regressions correlating doxorubicin dose with ejection fraction as percentage of initial value show declines in both groups (CHF: r=-0.41, p<0.05; asymptomatic: r=-0.52, p<0.001). The slope of the average fall of ejection fraction is 2.6% per course for those who ultimately developed the clinical syndrome and 2.9% for asymptomatic subjects. Each point represents the mean±SEM for the number of subjects tested before that monthly treatment. These results indicate that although the ejection fraction is sensitive to doxorubicin, it provides little or no ability to specifically discern those at risk for the development of clinically serious cardiotoxicity.

Cardiotoxicity also occurs after administration of other anticancer agents. Drugs that induce cardiotoxicity include all doxorubicin analogues (e.g., daunomycin hydrochloride, tetrahydropyranyl doxorubicin, epirubicin) and other anthraquinones (e.g., mitoxantrone hydrochloride). Several other antineoplastic agents (cyclophosphamide, fluorouridine, 5-fluorouracil, and mitomycin, among others) less frequently cause cardiotoxicity.18 Concurrent radiation therapy also potentiates this toxicity.9,19,20 Cancer therapy with interleukin-2 and tumor necrosis factor and other genetically engineered protein molecules with biological anticancer activity is also highly cardiotoxic. In fact, the dose-limiting side effects of many biotherapies may well relate to their cardiotoxicity.

A simple, sensitive, noninvasive, low-cost, office-based test for predicting who will and will not develop clinically relevant therapy-induced cardiac damage has been elusive. The search for a test useful for predicting doxorubicin-induced CHF has yielded a number of candidate procedures: 24-hour pulse measurement, a variety of electrocardiographic measurements, ballistocardiography, cardiac echography, Doppler blood flow studies, resting and exercise radionuclide ventriculography,21–25 and endomyocardial biopsy.26–28

An arbitrary cumulative doxorubicin dose limit of 550 mg/m² has been found to allow safe treatment of about 90% of patients treated with intermittent intravenous bolus doxorubicin.9,19,20 Not surprisingly, efficacy and toxicity of many drugs vary greatly on an individual basis. Some patients develop CHF secondary to intermittent bolus doxorubicin long before the 550-mg/m² total dose has been reached, whereas others tolerate substantially more drug with the development of significant cardiac disease. Administering the same total dose of doxorubicin in smaller weekly doses has long been associated with better doxorubicin cardiotoxicity than giving higher doses at 3- and 4-week intervals.29,30 Continuous infusion over 24, 48, 96, and 120 hours or longer has been demonstrated to allow higher cumulative doses of doxorubicin but significant toxicity to the heart still occurs, albeit usually after more than 700–1,000 mg/m².31

Regardless of how doxorubicin is administered, however, a finite risk of significant cardiac damage exists. Obtaining serial measurements of the RSA amplitude is easier, quicker, and less expensive than obtaining serial cardiac biopsies or ejection fraction determinations. Our data suggest that serial RSA determinations may provide a simple, easily reproducible, noninvasive earlier predictor of whether an individual patient is at risk of developing doxorubicin-induced CHF and is, therefore, likely to tolerate more or less than the recommended total doxorubicin dosage. Thus, a change in RSA may help signal when doxorubicin treatment should be stopped and when it may still be safe to continue. Additional prospective studies that increase the dose based on the RSA result are needed to rigorously test this hypothesis.

In this study, RSA amplitude fell progressively with increasing cumulative doxorubicin dose for the vast majority (88%) of the population of patients destined to develop clinically significant cardiac dysfunction. On average, the group of symptom-free patients, each of whom was followed for at least 2 years after the final doxorubicin dose or until death, did not show a significant RSA amplitude decrease during treatment. In our hands, the left ventricular ejection fraction proved less discriminating in separating patients fated to develop clinically relevant cardiotoxicity from those who would not. The ejection fraction declined significantly and equally in both groups of patients. Conclusions based on these results must be qualified because of the relative sparsity of RSA data. Data from Figures 4 and 5 indicate the longitudinal behavior of the RSA and
ejection fraction in each of those eight individuals who developed the clinical syndrome of doxorubicin-induced congestive cardiomyopathy. It is clear that more frequent measurement before each planned doxorubicin treatment would provide a more rigorous individual assessment of the utility of both tests. The frequency of ejection fraction determination was based upon common clinical practice. Because RSA results were unavailable for clinical decision making, it was often practically difficult to get the test done as frequently as would have been optimal. Our assessment of intertest variability before and after venipuncture in 25 age-matched control subjects is somewhat useful in assessing test result reproducibility; however, more rigorous and extensive assessment of test-to-test variability in cancer patients receiving doxorubicin awaits a larger prospective study of this methodology.

Various arbitrary cutoff points for absolute ejection fraction or for percent decline have proven to be of varying utility in the prospective evaluation of asymptomatic patients receiving doxorubicin, in part because of test-to-test variation. It is our technical interpretation that some of this test-to-test variability

FIGURE 4. Graph of the overall longitudinal behavior of the respiratory sinus arrhythmia (RSA) in each of the eight patients who developed doxorubicin-induced cardiomyopathy. The criterion of an RSA amplitude fall below 50% of that expected for age resulted in the proper classification of seven of eight patients. The sole failure of this cutoff was for patient 4, whose RSA amplitude started out at 125% of that expected for age and subsequently diminished substantially but not to 50% or less of that expected for age.

FIGURE 5. Graph of the overall longitudinal behavior of the left ventricular ejection fraction of each of the eight individuals who ultimately developed doxorubicin-induced cardiomyopathy. The index did not decline at all in four of the eight individuals, declined by less than 20% in two, and declined substantially in an additional two individuals. Correct classification of individuals by use of the ejection fraction, therefore, often depended on single low values in absolute terms.
in ejection fraction determination could be diminished by double gating the ejection fraction determination to the electrocardiographic signal and, concurrently, to the breathing cycle, which is responsible for substantial reproducible rhythmic changes in cardiac volume. Perhaps if ejection fraction determinations from similar points within the respiratory cycle were averaged separately, rather than averaged across all points in respiration, the breathing phase qualified test result would have less variability and ultimately prove more useful. In addition, the average difference in cardiac volume and/or ejection fraction across the respiratory cycle may itself yield interesting dynamic information.

The RSA has long been known to diminish with advancing age. The mechanisms involved in this decrease, however, have not been clearly established. Much of the difficulty in understanding the age-related diminution of the RSA is due to the complex and still poorly understood physiological basis for the RSA. A sizable body of research has accumulated that attributes the RSA to changes in autonomic nervous impulses reaching the heart. For instance, in anesthetized dogs, sympathetic and vagal nervous impulses to the heart have been found to fluctuate in synchrony with phrenic nerve impulses and diaphragmatic movement. Enhanced vagal tone has also been found to increase the RSA. On the other hand, studies of patients with diabetic autonomic neuropathy and after recent heart transplantation demonstrate that the RSA can persist in the denervated heart. These results point to the existence of an additional intrathoracic mechanism, possibly in accordance with Bainbridge’s 1920 explanation that the RSA is caused at least in part by the effect of intrathoracic pressure changes on the venous return to the heart and the response of an intracardiac reflex to these changes. Because in our current study patients did not demonstrate other evidence of autonomic neuropathy, changes in RSA seem to reflect the direct effect of doxorubicin on the heart muscle itself. The precise mechanism of how doxorubicin causes a decrease in the RSA remains to be established. Even cursory inspection of the stiffened myocardium of patients dying from this therapeutic complication, however, would lead one to conclude that this less compliant tissue would not behave similarly to normal myocardium when presented with small, regular, breathing-induced changes in venous return. In other studies, we have found that patients with normal autonomic function and cardiac abnormalities primarily characterized by decreased ventricular compliance, including concentric cardiac hypertrophy and hypertensive cardiomyopathy, also have markedly diminished RSAs.

Although cardiac biopsy is considered by many to be the gold standard for documentation of the presence and extent of doxorubicin-induced myocardial lesion, the procedure is expensive and invasive. For noninvasive measurement of doxorubicin-induced cardiotoxicity, radionuclide ventriculography has become the most commonly used screening test. Serial endomyocardial biopsies, proven to be reliable and useful, would have allowed us to compare the accuracy of the RSA and ejection fraction results in predicting subsequent heart failure. Such biopsies were not done because they are invasive and because few are routinely done outside centers with pathologists and cardiologists who have specific research interests in drug-induced cardiotoxicity. Although we were not able to perform exercise radionuclide ventriculography on our subjects, resting radionuclide ventriculography, the test most commonly used by medical oncologists to evaluate a patient’s risk for development of doxorubicin-induced CHF, was less effective than RSA amplitude determination in discriminating between patients with and without early preclinical progressive cardiomyopathy. This simple, noninvasive, 1-minute test seems to provide some useful screening information relevant to the common clinical conundrum posed by high-dose-intensity doxorubicin treatment, and it deserves careful further study.

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