Noninvasive early detection of anthracycline-induced cardiotoxicity in patients with hematologic malignancies using the phased tracking method

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Abstract

Anthracyclines are among the most effective and widely used anticancer drugs; however, their use is limited by serious cardiotoxicity. Early detection is necessary to prevent the high mortality rate associated with heart failure (HF). We evaluated cardiac function in 142 patients using conventional echocardiography and the phased tracking method (PTM), which was measured using the minute vibration and the rapid motion components, neither of which is recognized in standard M-mode nor in tissue Doppler imaging. For systolic function comparison, we compared left ventricular ejection fraction (LVEF) in conventional echocardiography with the average velocity of ventricular septum myocytes (V̇ave) in the PTM. The V̇ave of 12 healthy volunteers was 1.5 (m/s)/m or more. At baseline of 99 patients, there was a positive correlation between LVEF and V̇ave in all patients. There were no significant differences in baseline cardiac function between patients with and without HF. There was a negative correlation between the cumulative anthracycline dose and LVEF or V̇ave among all patients. We determined that V̇ave 1.5 (m/s)/m was equivalent to LVEF 60%, 1.25 (m/s)/m to 55%, and 1.0 (m/s)/m to 50%. During the follow-up period, there was a pathological decrease in LVEF (<55%) and V̇ave among all patients. We determined that V̇ave 1.5 (m/s)/m was equivalent to LVEF 60%, 1.25 (m/s)/m to 55%, and 1.0 (m/s)/m to 50%. During the follow-up period, there was a pathological decrease in LVEF (<55%) and V̇ave among patients with HF; decreases in V̇ave were detected significantly earlier than those in LVEF (P < 0.001). When V̇ave declined to 1.5 (m/s)/m or less, careful continuous observation and cardiac examination was required. When V̇ave further declined to 1.0 (m/s)/m or lower, chemotherapy was postponed or discontinued; thus, serious drug-induced cardiomyopathy was avoided in patients who did not relapse. The PTM was superior to echocardiography for early, noninvasive detection and intermediate-term monitoring of left ventricle systolic function associated with anthracycline chemotherapy, among patients with hematologic malignancies. The PTM was an effective laboratory procedure to avoid the progression to serious cardiomyopathy.
micrometers up to several hundred Hertz, which has neither been recognized in TDI nor standard M-mode, B-mode, 2D-strain echocardiography. These fine measurement characteristics and the rapid minute amplitude have allowed measurement of the fetal heart and the fetal descending aorta of normal and growth-restricted fetuses [7, 8].

The aim of this study was to compare changes in left ventricle cardiac parameters detected using the PTM with those obtained using conventional echocardiography in order to evaluate whether the PTM is superior for the detection of early anthracycline-induced changes in cardiac function in patients with acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), and malignant lymphoma (ML). We had experienced a case on the basis of the PTM measurement data, by adjusting the chemotherapy schedule as the development of serious cardiomyopathy was prevented [9] and improvement of prognosis is expected.

Methods

Study population

Twelve healthy volunteers and 142 patients with hematologic malignancies were eligible for the PTM and conventional echocardiography. Between August 1998 and August 2014, 128 consecutive patients underwent echocardiography and PTM to evaluate cardiac function. An additional 14 AML patients were examined after completion of chemotherapy in 2009. Patients were grouped according to the absence or presence of clinical heart failure (HF), no HF group and HF group, respectively (Table 1). Informed consent was obtained from all patients.

Chemotherapeutic protocols

Patients with ALL or ML underwent the modified CHOP protocol [10, 11], whereas those with AML underwent therapy with daunorubicin and cytosine-arabinoside [12–14]. Daunorubicin doses were converted to doxorubicin equivalents using a conversion factor of 0.56 that was the proposed equivalent tumor effect doses obtained with a standard protocol.

Echocardiography

Patients underwent comprehensive two-dimensional and Doppler echocardiographic examinations, which were performed by a single doctor using a EUB 655 ultrasound scanner (Hitachi, Ibaraki, Japan) and a SSD-500SV ultrasound scanner (ALOKA, Tokyo, Japan) in accordance with recognized standards. Left ventricular ejection fraction (LVEF) was calculated using modified Teichholz.

Phased tracking method

The ultrasound scanner was switched to the phased tracking mode. By referring to the M-mode image, which was constructed from the analog/digital (A/D) converted data, we manually preset two points, in the heart wall, between which, the ultrasonic beam was directed, as illustrated in Figure 1A. The principles of the PTM are illustrated in Figure 1B–D. Using the M-mode PTM as the parasternal long-axis view, we measured the M-mode image, electrocardiography, phonocardiogram, and small-amplitude velocity signals of less than a few micrometers of the interventricular septum (IVS) by tracking the results of the multiple points that normalized the speed of the change in thickness. Because the results obtained by the proposed method depend on the angle between the direction of

| Table 1. Characteristics of patients who underwent echocardiography (n = 142). |
|---------------------------------------------------------------|
|                                                                 |
|                  No HF group (n = 118)                          | HF group (n = 24)                           |
|                  ALL | ML | AML | No. pt. | ALL | ML | AML | No. pt. |
|-------------------|-----|-----|--------|-----|-----|-----|--------|
| Number of patients | 142 | 72  | 70     | 1   | 0   | 1   | 13     |
| Male              | 13  | 4   | 6      | 1   | 7   | 1   | 13     |
| Female            | 85  | 14  | 42     | 57  | 4   | 6   | 13     |
| Age at diagnosis, years |       |     |       | 21  | 55  | 54.7 |
| Average           | 58  | 51.5| 50.6   | 54.7| 21  | 55  | 54.7   |
| Median            | 62  | 51  | 48     | 58  | /   | /   | 58     |
| Range             | 16–89| 18–82| 18–80 | 14–88| /   | /   | 14–89 |
| Current age*, years |       |     |       | /   | /   | /   | 46–74 |
| Average           | 53  | 53  | 56.6   | 62.7| 27  | 64  | 54.2   |
| Median            | 54  | 50  | 57     | 66  | /   | /   | 50     |
| Range             | 14–86| 18–82| 20–84 | 15–93| /   | /   | 21–79 |

HF, heart failure; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; ML, malignant lymphoma, *, Final inspection age.
the velocity vector and the ultrasonic beam, the direction of the ultrasonic beam passing through heart wall was selected, so that the beam was almost perpendicular to each wall during the A/D conversion of several cardiac cycles. During the acquisition period, respiration was suspended. Figure 2 shows the superimposed estimates of the velocity signals \(v - (x_i, t)\) of each heart beat on the tracked points \(x_i - (t)\) on IVS during six heartbeats.
The vertical axis of these figures was inverted so that the negative value of the velocity, which is shown above the baseline, corresponds to the situation in which the object moves in the direction of the ultrasonic transducer on the chest wall. The resultant velocity signals are sufficiently reproducible for six heartbeat periods. The results were immediately visualized and output as shown in Figure 2.

**Statistical analyses**

The results are presented by the mean and median values. Paired and nonpaired two-tailed Student’s *t*-tests were used to compare parameters between the groups using the JMP11 statistical software (SAS Institute Inc., Cary, NC).

**Results**

The contractile force and contraction synchrony of myocardial cells was measured using the PTM. We analyzed the period between aortic valve opening and closing (as shown in Fig. 3) and calculated the average velocity (*V* _ave_) using the following equation:

$$\bar{V} = \frac{\sum_{n=1}^{N} \sum_{m=1}^{M} \Delta h(n;m)}{(f_2 - f_1)(n_2 - n_1)}$$

Of the 142 patients who underwent echocardiographic evaluations, 128 patients were sequentially examined during and after the completion of chemotherapy; however, patients sometimes missed examinations for deconditioning. Fourteen patients were evaluated only once, ten or more years long after completion of chemotherapy. Characteristics of the 142 patients who underwent echocardiographic evaluations are shown in Table 1. Patients were divided into two groups; no clinical cardiac symptoms (no HF group and cardiac clinical symptoms HF group). HF occurred in 11 male patients and 13 female patients, respectively (odds ratio 0.79 95% CI: 0.33–1.91). There were no significant differences between patient characteristics in the ALL, AML, and ML groups, with the exception of the mean age of patients with ALL, which was 21 years at the time of diagnosis, approximately 30 years younger than the average age of patients in the other groups.

Prior to treatment, baseline LVEF was positively correlated with *V* _ave_ (*r* = 0.7468; Fig. 4). One hundred and eighteen patients had no clinical HF, with a maximum anthracycline dose of 2205 mg/m². Among the 24 patients in HF group, the minimum cumulative anthracycline dose associated with development of HF was 241 mg/m². There were no significant differences in baseline cardiac function between no HF group and HF group (Table 2).

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**Figure 3.** Average velocity of change in thickness for determination.

**Figure 4.** Correlation with left ventricular ejection fraction and average velocity at baseline.
Baseline cardiac functions between patients with no clinical cardiac symptoms (no heart failure [HF] Group) and those with congestive heart failure clinical symptoms (HF Group).

| Echocardiography | No HF group | HF group | P  |
|------------------|-------------|----------|----|
| CTR %            | 47 ± 0.06   | 46.3 ± 0.04 | 0.5|
| QTC, sec         | 0.42 ± 0.039| 0.4225 ± 0.026| 0.6|
| IVC, mm          | 11.12 ± 2.86| 10.7 ± 1.85 | 0.62|
| AO, mm           | 19.64 ± 3.14| 19.7 ± 2.21 | 0.64|
| LA mm            | 30 ± 5.09   | 29.7 ± 3.52 | 0.52|
| LVEF             | 0.753 ± 0.063| 0.76 ± 6.6 | 0.84|
| FS               | 0.374 ± 0.027| 0.378 ± 5.4 | 0.06|
| PEP/ET           | 0.253 ± 0.119| 0.31 ± 0.082 | 0.96|
| A/E              | 0.884 ± 0.272| 0.84 ± 0.386 | 0.7|
| The PTM          | 2.427 ± 0.971| 2.39 ± 0.972 | 0.94|
| Vave (m/s)/m     | 21.89 ± 17.64| 24.7 ± 17.64 | 0.09|

AO, aortic valve diameter; CTR, cardiothoracic ratio; EA, left ventricular flow; FS, fractional shortening; IVC, inferior vena cava diameter; LA, left atrial diameter; LVEF, left ventricular ejection fraction; PEP/ET, pre-ejection time/ejection time; PTM, phased tracking method; QTC, correction QT time; SD, standard deviation; Ths/thd, ratio of thickness in the systolic and in the diastolic phase; Vave, average velocity of cardiomyocytes; Vmax, maximum velocity of cardiomyocytes.

Table 3 shows the correlation between the cumulative anthracycline dose and LVEF or Vave. Both LVEF and Vave decreased with increasing anthracycline cumulative dose in all patients. However, in HF group, Vave decreased at a significantly smaller cumulative dose point than did LVEF (P = 0.003). Vave also significantly decreased 2–3 years after the completion of chemotherapy (P = 0.01); however, among patients who survived more than 5 years after the completion of chemotherapy, those in no HF group had recovered cardiac function, whereas cardiac function remained depressed in HF group. In no HF group, LVEF was not shown the reduction but Vave showed decreased (0.001), also, in HF group, Vave was shown a significant declined than LVEF (0.01) after completion of chemotherapy.

In accordance with the historical proposal of cardiotoxicity definition [14, 15], Vave 1.5 (m/s)/m was comparable to LVEF 60%, Vave 1.25 (m/s)/m to LVEF 55%, and Vave 1.0 (m/s)/m to LVEF 50%, at 1 and 12 months before the onset of HF [2, 16] (Fig. 4). As shown in Table 4, Vave declined significantly earlier than did LVEF. Figure 5 shows the correlation between %LVEF and Vave during the courses of chemotherapy. The value of the linear slope in Fig. 5 (r = 0.6) was lower than that in Fig. 4 (r = 0.74). The effect of myocardial disturbance on chemotherapy was more sensitive in terms of the Vave than the LVEF.

In Table 5, among 12 healthy volunteers, 99 patients before chemotherapy with no heart disease at baseline, and 26 patients with hematomic disease with neither malignancy nor heart disease, the average value of Vave was 2.503 (m/s)/m, with maximum and minimum values of 5.117 (m/s)/m and 0.99 (m/s)/m, respectively.

10% had Vave ≤ 1.5 (m/s)/m and 2.5% had Vave ≤ 1.0 (m/s)/m (Fig. 6A). Figure 6B shows the values of Vave in 520 examinations during the course of the study. Among this group, 20 of 49 patients (40.8%) with Vave ≤ 1.0 (m/s)/m developed HF, and 14 of these patients with Vave ≤ 0.5 (m/s)/m soon developed severe HF.

Table 6 shows data regarding the sensitivity and specificity of Vave. Powerful and effective action of the heart is sustained by synchronization of cardiac myocytes. In Figure 2B, the mottled pattern of a visualized color-coded velocity signal schematic shows disturbance of the continuous smooth movement at the left ventricular septum, during opening and closing of the aortic valve. Cut-off value setting of faster velocity is needed further study.

Table 3. Correlation between the cumulative anthracycline dose and the cardiac functions of left ventricular ejection fraction and average velocity of cardiomyocytes.

| Cumulative DOX Dose (mg/m²) | No heart failure (HF) group | HF group |
|-----------------------------|-----------------------------|----------|
|                            | LVEF (%) Mean ± SD | Vave (m/s)/m Mean ± SD | n | LVEF (%) Mean ± SD | Vave (m/s)/m Mean ± SD | n |
| 0                           | 75.3 ± 6.3 | 2.43 ± 0.97 | 87 | 76 ± 6 | 2.43 ± 0.97 | 18 |
| 100                         | 74 ± 5.9  | 2.075 ± 0.904 | 42 | 73.1 ± 5.1 | 1.851 ± 0.749 | 14 |
| 200                         | 74.7 ± 6.2| 2.14 ± 0.853 | 46 | 71.3 ± 6.9 | 2.080 ± 0.815 | 16 |
| 300                         | 73.5 ± 5.3| 2.008 ± 0.637 | 46 | 68.8 ± 6.8 | 1.879 ± 0.676 | 17 |
| 400                         | 73 ± 5.7  | 2.13 ± 0.665 | 44 | 68.8 ± 9.9 | 1.89 ± 0.924 | 18 |
| 500                         | 68.8 ± 6.4| 2.157 ± 0.775 | 46 | 66.5 ± 8.2 | 1.75 ± 0.459 | 15 |
| 600                         | 71 ± 1.1  | 2.2 ± 0.086 | 41 | 61.8 ± 13.6 | 1.32 ± 0.64 | 17 |
| Completion of CT after 2–3y | 71 ± 10.99| 1.82 ± 0.805 | 45 | 54 ± 13.9 | 1.096 ± 0.805 | 13 |
| Completion of CT after 5 or more years | 71 ± 9.2 | 1.99 ± 0.82 | 50 | 50.9 ± 13.9 | 0.95 ± 1.016 | 10 |

CT, chemotherapy; DOX, doxorubicin; SD, standard deviation; LVEF, left ventricular ejection fraction; Vave, average velocity of cardiomyocytes.
When $V_{ave}$ values fell to $\leq 1.5$ (m/s)/m, the rest period was extended to allow recovery of at least $V_{ave} 1.5$ (m/s)/m, then the following treatment was initiated. For cases in which $V_{ave}$ decreased <1.0 (m/s)/m, we canceled additional chemotherapy treatment. Even if myocardial damage is expressed, it is possible to long-term survival if not experienced recurrence ($P = 0.0001$) in Table 7. Among patients who experienced recurrence, cardiac function decreased and patients developed fatal cardiomyopathy; however, patients who did not relapse did not suffer fatal cardiomyopathy, and some of them recovered [9].

The summary of the aforementioned results and our proposal for clinical treatment of patients in each group are shown in Table 8. Examples of the color-coded image for each grade of velocity in Table 8 are shown in Figure 7.

### Discussion

Anthracyclines were originally introduced in the late 1960s as chemotherapeutic agents. They are extremely effective drugs for the treatment of leukemia and a wide variety of solid tumors. In patients undergoing anthracycline therapy, dose-dependent myocardial impairment has been described in 23–74% of cases, with a high incidence of

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**Table 6.** The determination of sensitivity and specificity for the detection of congestive heart failure by the Vave with the phased tracking method.

| Vave (m/s)/m | Sensitivity | Specificity |
|--------------|-------------|-------------|
| 1.25         | 0.98        | 0.96        |
| 1            | 0.87        | 0.96        |
| 0.5          | 0.64        | 1           |
HF or fatal complications in 5–19% of cases [2, 3, 17–21]. In contrast, there are no evidence-based guidelines for monitoring cardiotoxicity in adult patients with cancer [22, 23]. Currently, echocardiography and multigated radionuclide angiography are the most commonly used techniques for noninvasive baseline and serial assessment of LVEF [3, 19, 23, 24]. Current echocardiography guidelines focus on quantitative measurements of LVEF, rather than visual assessment [2, 17–19, 22, 25–27]. The fundamentals, strengths, and limitations of these techniques were the topic of a recently published consensus statement [28, 29]. The high-resolution Doppler measurement, showed the systolic heterogeneity of subendocardial myocardial ischemia in normal subjects [1].

The PTM, which was employed in this study, has been applied to clinical studies by many researchers, that is, noninvasive evaluation of the myocardial property of contraction and relaxation [5, 30, 31], elasticity of the arterial wall [32–36], and fatal cardiac or artery [7, 8, 37]. Although in this study, we reported only V ave during systolic time at the left ventricular septum, we hypothesize that the development of more detailed myocardial damaging process becomes clear by analyzing the continuous temporal relationship with V ave, V max, and color image. The nature of cardiac tissue that exhibits low levels of antioxidative enzymes, such as superoxide dismutase and catalase, make it more susceptible to redox oxidative stress (ROS)

Table 7. Survival of patients after V ave decreased below 1.0 (m/s)/m led to the cessation of chemotherapy versus the survival of relapse-free or relapsed patients.

| Case Number | Survival time after cessation of chemotherapy | Survival time after relapse |
|-------------|-----------------------------------------------|---------------------------|
|             | Average | Mean | Range      | Average | Mean | Range      |
| Relapse-free patients | 6       | 131 months+ | 158 months + | 52 months | ←163 months + |
| Relapsed patients    | 18      | 24 months | 17 months | 1 months–88 months | 4 months | 2 months | 7 days–17 months |

Table 8. The summary of the aforementioned results and our proposal for clinical treatment.

| V ave (m/s)/m | Cardiotoxicity | Medical care attitude          |
|---------------|---------------|-------------------------------|
| Grade 0 ≥1.5  | No            | No                            |
| Grade 1 >1.5–2.0 | Slightly   | Careful observation is required |
| Grade 2 <1.0–2.0 | Moderate | Treatment postponed or discontinuation is desirable. |
| Grade 3 <0.5  | Severe        | Fatal cardiomyopathy is tight. |

Figure 6. The values of V ave. (A) The average value of V ave of 12 healthy volunteers and 99 patients before chemotherapy was 2.503 (m/s)/m, with maximum and minimum values of 5.117 (m/s)/m and 0.99 (m/s)/m, respectively. (B) The average values of V ave in 520 examinations during the course of the study was 2.012 (m/s)/m, 1.0 (m/s)/m or less in 20 patients, 0.5 (m/s)/m or less was 14 patients.
generation and accumulation of oxidative stress. The major mechanism of chemotherapy-induced cardiotoxicity involves the generation of ROS. In turn, elevated ROS causes cellular damage and alternation responses [38]. Therefore, measurement with noninvasive the PTM, which is measured with small-amplitude velocity signals of less than a few micrometers, before and after chemotherapy helps to prevent cardiotoxicity.

Careful observation is required to detect decreases of more than 1.0 (m/s)/m in such patients to consider treatment delay or cancelation in order to avoid lethal cardiotoxicity. To circumvent the development of HF, early detection of drug-induced changes in cardiac function is essential for preventive intervention. Careful surveillance using the PTM could ensure early detection and timely management of such cardiotoxicity.

**Conclusion**

The PTM was superior to echocardiography for early, noninvasive detection and intermediate-term monitoring of left ventricle systolic function associated with anthracycline chemotherapy in patients with hematologic malignancies. We found that the PTM is a valid laboratory procedure that may help avoid progression to serious cardiomyopathy.

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**Conflict of Interest**

The authors declare no conflicts of interest.

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