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● *Original Contribution*

LEFT VENTRICULAR TRANSMURAL SYSTOLIC FUNCTION BY HIGH-SENSITIVITY VELOCITY MEASUREMENT "PHASED-TRACKING METHOD" ACROSS THE SEPTUM IN DOXORUBICIN CARDIOMYOPATHY

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Abstract—The clinical usefulness of doxorubicin is limited by doxorubicin-induced cardiomyopathy (DoxCM). The prognosis of this disorder is poor, and a sensitive noninvasive method for detection of DoxCM is strongly required. In this study, we examined if the transmural systolic function (TSF) obtained by the novel phased-tracking method is capable of supplying new information on DoxCM. A total of 18 healthy subjects and 30 patients with acute lymphoblastic leukemia were examined for TSF, as defined by the transmural profile of % thickening obtained by measuring the velocity at each preset point of 0.75-mm intervals. The total number of measurements was 94. In the patients, a decrease in both the peak velocity and the systolic layer thickening was observed, even in the subclinical phase of the normal ejection fraction. For healthy subjects, systolic thickening occurred in the left ventricular (LV) side of the interventricular septum (IVS), and was characterized by a sharp single-peak configuration of the profile. For the patients, however, the peak became dull and/or unclear, which indicates that a change in transmural functional distribution occurred. We concluded that the TSF is a useful measure for diagnosis of the early phase of DoxCM. (E-mail: koiwa@intl.med.tohoku.ac.jp) © **2002 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Doppler measurement, Intramyocardial velocity, Myocardial layer thickening, Transmural systolic function, Doxorubicin cardiomyopathy.**

INTRODUCTION

Doxorubicin (adriamycin) is an antineoplastic agent effective against a wide range of solid or hematologic malignancies. Its use is, however, often limited by cardiomyopathy (DoxCM) (Lipshultz et al. 1991; Steinherz et al. 1991). As for the diagnosis of DoxCM, endomyocardial biopsy has been considered as the "gold standard" for evaluating the magnitude of the induced damage. This invasive technique, however, can hardly be used in cases of heart failure or for long-term follow-up, and the results may be contaminated by biopsy error (Dunn 1994). Moreover, it has been reported that biopsy specimens from the right ventricular (RV) side of the intraventricular septum (IVS) are not as sensitive for DoxCM as specimens from the LV side of the IVS. This indicates that we should perform left heart catheterization, although this is usually considered as being beyond the bounds of daily clinical practice (Mortensen et al. 1986). A recent approach to protection against DoxCM by the parallel use of antioxidants shows some therapeutic promise (Morishima et al. 1998; Siveski-Iliskovic et al. 1995). This possibility of eliminating the cardiotoxic effects further highlights the need to develop noninvasive methods for long-term repetitive monitoring, notwithstanding the many approaches, such as exercise echocardiography, radionuclide angiography and the Doppler technique (Choi et al. 1988; Marchandise et al. 1989; Palmeri et al. 1986; Weesner et al. 1991). Practically, as detailed in several reviews (Doroshow 1991; Dunn 1994), no adequate diagnostic method for estimating subclinical myocardial damage in daily clinical prac-

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Table 1. Experimental-results on the transmural systolic thickening

Reference	Materials preparation	Contribution to the total wall thickening (mean ± SD)
Gallagher et al. 1985	conscious dog	inner 1/2 = total-outer: 71 ± 9% outer 1/2: 29.9 ± 9%
Myers et al. 1986	open chest dog	inner 1/3: 58% middle 1/3: 25% outer 1/3: 17%
Sabbah et al. 1981	open chest dog	endocardium (theoretical) 1/2:83% epicardium (theoretical) 1/2:17%
Myers et al. 1984	dog heart	inner 1/2: 71% outer 1/2: 29%
Bolli et al. 1984	conscious dog	inner 1/3: 46 ± 4% middle 1/3: 27 ± 2% outer 1/3: 19 ± 2%

In experimental studies, the number of layers was limited to two or three. The myocardium on the LV side (inner, endocardium or inner + middle in reports) showed greater thickening during systole, which corresponds to the existence of functional heterogeneity (physiological heterogeneity) across the wall. The term "theoretical" in (3) means estimation from theoretical drawing.

tice has yet been established, despite the fact that a variety of parameters have been proposed. Lipshultz et al. (1991) stressed that increased LV afterload (measured as end-systolic wall stress) due to the reduction in wall thickness was a key factor for determining the clinical course of 115 children at 1 to 15 years from the end of treatment. Their conclusion that the increase in afterload might have occurred primarily due to impaired myocardial growth by doxorubicin injection is a persuasive example of the pathophysiology of this DoxCM.

It has been confirmed, mainly in experimental models, that transmural systolic functional heterogeneity exists in the normal heart (physiologic heterogeneity) because the dominant layer of thickening lies in the heart wall on the LV side (Gallagher et al. 1985; Myers et al. 1986; Sabbah et al. 1981). Table 1 summarizes the heterogeneous TSF in previously reported experiments. The observed change of magnetic resonance image (MRI) tagging in the endocardium, myocardium and epicardium with regard to this physiologic functional heterogeneity in hypertrophic cardiomyopathy or myocardial infarction has been considered as being important in interpretation of the pathophysiology of the disease (Bogaert et al. 1999; Dong et al. 1994). For patients under doxorubicin treatment, however, an approach to monitoring of the myocardial damage from the viewpoint of transmural heterogeneous behavior has never been examined. This is despite the fact that the morphological damage, including fibrous thickening, has been more pronounced in the LV side of the IVS in patients (Mortensen et al. 1986). This suggests that the histological change in the myocardium occurs heterogeneously across the wall and generates further complexity in the pathophysiology of this disease.

At present, three diagnostic methods (tissue Doppler imaging or TDI, integrated backscatter, and magnetic resonance imaging or MRI tagging) are considered to be potentially useful for evaluating transmural functional heterogeneity (Colonna et al. 1999). However, several problems remain to be solved. For example, for myocardial slow motion and change in wall thickness, MRI tagging is limited to several mm in the spatial resolution and several tens of ms in the time resolution (Bogaert et al. 1999; Dong et al. 1994; Maier et al. 1992). Conventional 2-D color flow mapping instruments have been modified to acquire low-frequency large-amplitude Doppler signals in TDI, and slow tissue motions toward the transducer and away from the transducer are, respectively, color-coded in red and blue on the B-mode or M-mode echocardiographic image (Donovan et al. 1995; Gorcsan et al. 1997).

Kanai et al. (1996) have reported a novel ultrasonic-based method to accurately track the large motion of a point preset in the myocardium, based on both the phase and magnitude of the signal reflected at the point. By this method, velocity signals of small amplitude, $v(t; x_i)$, of a point i at a depth of x_i in the ventricular wall, which are less than several μm and up to about 100 Hz on the large motion resulting from a heartbeat, can be detected with sufficient reproducibility. By integrating the difference in the resulting velocity signals at two preset points along the ultrasonic beam, a minute change in thickness of several tens of μm has been detected with high temporal and spatial resolution (Kanai et al. 1997). The μm-order velocity of the myocardial thickening can be separated from the large wall motion by this method. In patients with aortic valve stenosis, for example, the transmission of vibration across the septum has been demonstrated by this method (Kanai and Koiwa 2001). That is, the systolic ejection murmur at the aortic root was transmitted heterogeneously and regionally to the intramyocardial

preset points in the basal region of the LV side of the septum.

From histological examinations using doxorubicin-injected rabbits, the TSF has been confirmed to be closely related to the magnitude of myocardial damage (Koiwa et al. 1998). One of the advantages of this method is that it yields information on the patient's transmural functional heterogeneity of the ventricular wall with extremely high resolution compared with previous methods. Thus, we aimed to clarify if this novel Doppler method, the phased-tracking method, can be of use for diagnosis in patients with DoxCM.

METHODS

Subjects

We examined the following subjects from April 1995 to March 1999: 18 healthy subjects (25.7 ± 7.9 years old; male) and 30 patients with acute lymphoblastic leukemia (32.9 ± 11.8 years old; 17 male and 13 female) who were receiving mitoxantrone hydrochloride (HCl) injection as a part of their combined chemotherapy treatment. Among these subjects, 4 healthy volunteers and 9 patients were examined repeatedly during the study period, the total number of measurements being 94 (24 times for healthy subjects and 70 times for patients). During this period, 5 patients; 2 died from relapse of the malignancy and 3 died from DoxCM. Except during the terminal stage of these patients, measurements were carried out at an outpatient clinic. The dose of mitoxantrone HCl was converted to an equivalent dose of doxorubicin. The value of the administered dose normalized by body surface area (Dose/BSA) was 480.9 ± 89.0 mg/m^2.

Measurement of conventional LV function in the routine echocardiographic method

Using ultrasonic diagnostic equipment (Toshiba, SSH 160A, Tokyo, Japan), the following seven parameters were measured by a conventional echo Doppler method during the follow-up period: 1. LV end-diastolic diameter (LVDd); 2. LV end-systolic diameter (LVDs); 3. wall thickness of the interventricular septum (IVSWT) at end-diastole; 4. ejection fraction (EF); 5. peak velocity of E-wave (E); 6. peak velocity of A-wave (A) and 7. E:A ratio.

Measurement of myocardial layer thickening

By taking into consideration the results of an MRI tagging study that showed that the septum of the ventricle exhibited far less 3-D movement during the cardiac contraction compared with other regions of the anterior wall, posterior wall, and apex (Maier et al. 1992), TSF was obtained at the basal anteroseptal segment of the IVS, where the ultrasonic beam was projected at an angle almost normal to the IVS. That is, the direction of the ultrasonic beam passing through the measurement points was selected in the longitudinal, B-mode cross-sectional image so as to be almost perpendicular to the IVS during the measurements. Just after the selection, the direction of the ultrasonic beam was fixed and the quadrature-demodulated signal of the RF signal was A/D converted during several heartbeats. By selecting the ultrasonic beam passing through the measured points so that it is perpendicular to the heart wall in the cross-sectional images along the conventional longitudinal axis, it has been experimentally confirmed that the measured point is almost perpendicular to the heart wall during the measurements (Kanai et al. 1996).

The principle of the phased-tracking method, including the theoretical and *in vivo* evaluations for the myocardial layer thickening rate, has been detailed previously (Kanai et al. 1996, 1997). In brief, radiofrequency (RF) pulses with an angular frequency of $\omega_0 = 2\pi f_0$ are transmitted at time intervals of ΔT from an ultrasonic transducer on the chest wall. The phase difference, $\Delta\theta(x;t)$, between the phase $\theta(x;t)$ of the quadrature-demodulated signal of the received signal, $y(x;t)$, and the phase $\theta(x;t + \Delta T)$ of the quadrature-demodulated signal of the subsequently received signal, $y(x;t + \Delta T)$, is given by:

$$\Delta\theta(x;t) = \theta(x;t + \Delta T) - \theta(x;t) = \frac{2\omega_0}{c_0}\Delta x(t), \quad (1)$$

where $\Delta x(t) = x(t + \Delta T) - x(t)$ is the movement of the object during the period ΔT around time t, and c_0 is the acoustic velocity in the human body. In our examination, the period ΔT was set at 250 μs. Because the maximum value of the acceleration in the IVS is about 4 m/s^2 (Kanai et al. 1996), the velocity of the IVS changes by 0.001 m/s at most, which is 1/400 of the higher limit of the measurable velocity (0.4 m/s), for the short period ΔT of 250 μs. Thus, the velocity of the IVS is assumed to be constant during the pulse-repetition interval ΔT. By dividing the movement Δx by the period ΔT, the average velocity $v(t + \Delta T/2)$ of the object during the period ΔT is given by:

$$v\left(t + \frac{\Delta T}{2}\right) = \frac{\Delta x(t)}{\Delta T} = \frac{c_0}{2\omega_0} \cdot \frac{\Delta\theta(x;t)}{\Delta T}. \quad (2)$$

The phase difference $\Delta\theta(x;t)$ is accurately determined by the constraint least squares approach based on the complex cross-correlation between $y(x;t)$ and $y(x;t + \Delta T)$, under the condition that the signal waveforms do not change except that their phase values change during the period ΔT. It is impossible to accurately determine

the true lag value from the complex correlation function, which is derived from the standard normalized mean squared difference between the quadrature-modulated signals of the successively received signals (Kanai et al. 1996). However, the introduction of the constraint is effective for the determination of the lag between these complex signals. By multiplying the resultant velocity *(t + ΔT/2)* by the period ΔT, the next depth *x(t + ΔT)* of the object is estimated by:

$$x(t + \Delta T) = x(t) + \hat{v}\left(t + \frac{\Delta T}{2}\right) \times \Delta T, \qquad (3)$$

Using the resultant signal *x(t + ΔT)*, the displacement of the object (the position of the region of interest or ROI) in the heart wall is successfully tracked, and then the velocity signal $v|\mathrm{Ax}(t)$ on the large motion due to the heartbeat is accurately measured.

In practice, a high-speed A/D converter with a large-scale memory was employed to analyze the complex signal resulting from the quadrature modulation of the signal received by a sector-type ultrasonic transducer connected to standard ultrasonic diagnostic equipment. The employed ultrasonic frequency, f_0, was 3.75 MHz, and the repetition interval ΔT of the pulses was 222 μs. The resultant real and imaginary signals of the demodulated Doppler signal were simultaneously A/D converted with a 2-channel 12-bit A/D converter at a sampling rate of 1 MHz. The initial positions of the multiple sampling points across the wall were manually set al.ong the ultrasonic beam at the timing of the peak *R* in the electrocardiogram (ECG). The lower limit of the resolution of the change in layer thickness was 0.5 μm, and the higher limit of the measurable velocity was about 0.4 m/s, which was determined by aliasing with the conventional Doppler system (Kanai et al. 1997).

Measurement of TSF

By defining the systole as the period between the onset of the Q wave in ECG and the second heart sound, the following seven parameters of TSF were measured: 1. maximum velocity (peakV) and 2. maximum negative velocity (negV) of the transmural preset points; 3. the profile of the percent of thickening, defined by the systolic thickness divided by the thickness at the timing of the *R* wave, at each layer across the IVS (% thickening); 4. maximum percent of thickening of the layer across the wall at systole (max%Tkn); 5. the number of functioning layers showing thickening greater than 110% at systole (#Nf); 6. percent of the number of functioning layers across the wall (%Nf); and 7. percent of the nonfunctioning layers at systole (%Nn).

Reproducibility of parameters of TSF

To evaluate the observational variability of the measurement of TSF, two independent observers measured the parameters of TSF at intervals of approximately 5 min for 22 subjects (9 healthy and 13 patients) to evaluate the interobserver variability. The repeatability of TSF was assessed in 19 subjects (8 healthy and 11 patients) by two sequential measurements approximately 30 min apart.

Statistics

All values are expressed as mean ± SD, unless otherwise indicated. Analysis of variance (ANOVA) was used to assess the difference in each variable between healthy subjects and patients. When statistically significant results were found, *post hoc* individual comparison was made with Bonferroni's test. Simple regression analysis was used to determine if it was possible to estimate the magnitude of each variable from the routine ECG method and TSF or Dose/BSA. A two-tailed *p* value of less than 0.05 was considered to indicate statistical significance. Multiple stepwise regression with the forward-increment method was used to examine the links between the max%Tkn, peakV, negV or %Nf and variables of age, body length, body weight, systolic blood pressure, diastolic blood pressure, heart rate (HR), LVDd, LVDs, IVSWT, EF, and Dose/BSA (F-to-enter value > 4.00).

RESULTS

There was good agreement in the interobserver variability for TSF, namely, the SD accounted for 7%, 10%, 8%, 8% and 11% of the measured max%Tkn, peakV, negV, %Nf and %Nn, respectively. The repeatability was 18%, 15%, 19%, 12% and 20% in SD, respectively, for each of the above parameters. No significant difference in each parameter was observed between the first and second measurements, nor between operators.

Table 2 shows the baseline characteristics in healthy subjects and patients. Figure 1a shows an image of the TSF at the septum for a healthy subject (a 22-year-old man) and Fig. 1b shows that for a patient (a 25-year-old man) undergoing treatment with a mild dose of doxorubicin (360 mg/m^2 of BSA), where EF = 64%. From top to bottom, Fig. 1 shows the M-mode image of the echocardiography, ECG, superposition of the velocity signals at all preset points (13 points in Fig. 1a and 15 points in Fig. 1b), and the change in thickness of each layer where the RV surface is flat. In the superposition of the velocity signals from each preset point within the myocardial layers, the difference in velocities corresponds to the change in thickness of the layer; they were much more remarkable for the healthy subject than for the patient at

Table 2. Clinical features and baseline characteristics in patients with doxorubicin injection and healthy subjects

	Patients	Healthy subjects	*p* value
Age (y)	32.8 ± 11.2	25.7 ± 7.9	†
Body length (cm)	161.4 ± 6.5	170.9 ± 5.4	‡
Body weight (kg)	58.8 ± 9.0	65.0 ± 6.7	†
BSA (m^2)	1.6 ± 0.1	1.8 ± 0.1	†
Systolic BP (mmHg)	118.7 ± 15.8	123.9 ± 8.5	*
Diastolic BP (mmHg)	78.0 ± 11.7	72.7 ± 7.5	*
HR (1/min)	81.1 ± 16.1	68.6 ± 8.8	‡
(1) LVDd (mm)	48.5 ± 5.3	48.3 ± 3.4	
(2) LVDs (mm)	32.1 ± 7.1	30.0 ± 3.9	*
(3) IVSWT (mm)	8.3 ± 1.8	8.9 ± 1.2	*
(4) EF (%)	57 ± 1	65 ± 8	†
(5) E (m/s)	0.6 ± 0.2	0.8 ± 0.2	*
(6) EA	1.3 ± 0.5	1.6 ± 0.3	†

Each value is expressed as mean ± SD. The meanings of terms (1)–(6) are described in the beginning of Methods section. *$p < 0.05$, †$p < 0.01$; ‡$p < 0.001$.

systole. As for the magnitude of the systolic thickening at each layer, as shown at the bottom of Fig. 1a, there was a difference across the wall, especially in the healthy subject; namely, the magnitude was larger at the middle to LV side of the septum during early and late systole. That is, there was physiological heterogeneity across the wall (physiological heterogeneity) in the healthy subject. For the patient, however, as shown at the bottom of Fig. 1b, the peak thickening and thickening rate were much smaller than those of the healthy subject.

The transmural systolic thickening (%) in each third of the septum from the RV side to the LV side was 27.6 ± 2.6%, 31.8 ± 2.4%, and 40.4 ± 3.0%, respectively, in healthy subjects. Figure 2 shows a profile of the heterogeneous thickening across the wall for healthy subjects.

The maximum of the percent of thickening of the layer across the wall at systole, max%Tkn, in the healthy subjects was 223 ± 46%, that is, from 300% to 180%, and no thinning was observed. The parameters on transmural functional heterogeneity derived from the TSF showed significant differences between healthy subjects and patients as summarized in Table 3. Maximum velocity (peakV), maximum negative velocity (negV) at the preset point, and max%Tkn were larger in healthy subjects. For patients, on the other hand, the percent of the number of functioning layers across the wall, %Nf, was smaller and the percent of the nonfunctioning layers at systole, %Nn, was larger.

Figure 3 shows the relationships between the ejection fraction (EF) and the four parameters (%Nf, max%Tkn, negV, and peakV) in the TSF. The lower limit of the normal range of EF (mean-SD value in our university hospital) and the mean-SD values of TSF from healthy subjects in this report are expressed by a solid line. These relationships are summarized as follows:

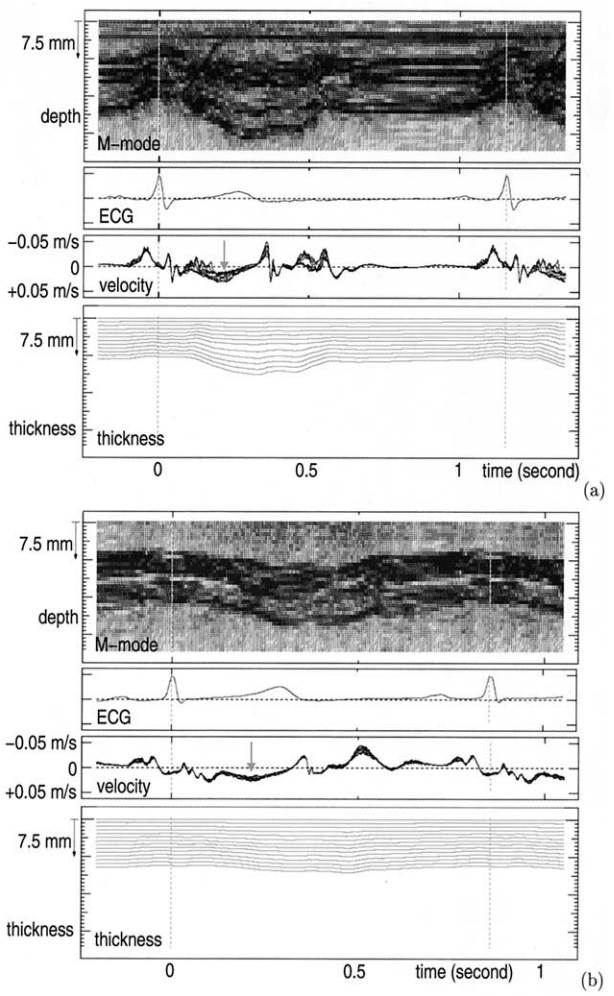

Fig. 1. The thickening of each myocardial layer during the cardiac cycle. (a) A healthy 22-year-old man; (b) a 25-year-old man under doxorubicin treatment. From top to bottom in each figure, M-mode echocardiography, ECG, superposition of velocity signals at each preset point at different depths (0.75 mm interval; the first point was set at the right ventricular endocardial surface), the changes in thickness of the transmural layers during the cardiac cycle, where the RV surface of the septum was set as no movement to facilitate understanding of the differences among layers. The vertical dotted line indicates R-wave timing of ECG. The arrow shows the timing of the maximum velocity during systole.

$$\text{peakV (m/s)} = 0.005 + 0.151 \times \text{EF(\%)}, \quad r = 0.38,\ p < 0.01$$

$$\text{negV (m/s)} = 0.006 + 0.001 \times \text{EF(\%)}, \quad r = 0.32,\ p < 0.01$$

$$\text{max\%Tkn (\%)} = 73.9 + 1.79 \times \text{EF(\%)}, \quad r = 0.62,\ p < 0.01$$

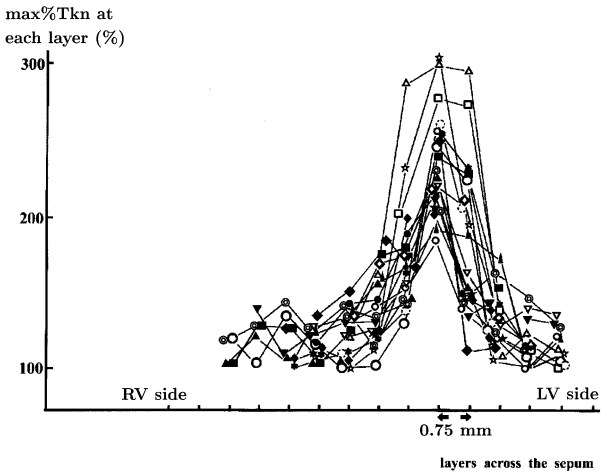

Fig. 2. Profiles of max%Tkn across the septum in healthy subjects. The magnitude of thickening is different among layers across the wall and the layer of maximum thickening extends from the middle wall to LV side. The maximum systolic thickening showed values approximately 200% larger.

$$\%\mathrm{Nf}\ (\%) = 23.2 + 0.65 \times \mathrm{EF}(\%),$$

$$r = 0.31,\ p < 0.01.$$

There were significant relationships between EF and TSF, and even the r value was not so strong. As plotted in the right lower quadrant in each part of Fig. 3, many patients maintained a normal EF despite the fact that the TSF was reduced compared to the normal range (horizontal solid line). This indicates that the deterioration of the TSF precedes the conventional global ventricular function in many cases.

Table 3. Seven parameters of TSF derived from the velocity measurement at intramural preset/points in patients with doxorubicin injection and healthy subjects

	Patients	Healthy subjects	p value
1. max % Tkn	169 ± 34	223 ± 46	‡
2. peakV (m/s)	0.024 ± 0.010	0.034 ± 0.007	‡
3. negV (m/s)	0.037 ± 0.014	0.048 ± 0.014	†
4. #Nf	6.60 ± 2.10	8.88 ± 2.31	‡
5. %Nf (%)	57.6 ± 19.3	76.9 ± 11.6	‡
6. #Nn	3.4 ± 1.9	2.5 ± 1.7	*
7. %Nn (%)	28.2 ± 14.1	20.5 ± 11.8	*

1. max%Tnk = maximum thickening rate of the myocardial layer across the septum; 2. peakV = peak velocity during contraction phase at a preset point in the myocardial wall; 3. negV = peak negative velocity during relaxation phase at a preset point; 4. #Nf = the number of functioning layers showing thickening at systole at the midtiming of the first and second heart sounds; 6. #Nn = the number of nonfunctioning layers; 5. %Nf and 7. %Nn = the percentage of each parameter (#Nf, #Nn) through the septum; p value = $^{*}p < 0.05$; $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.001$.

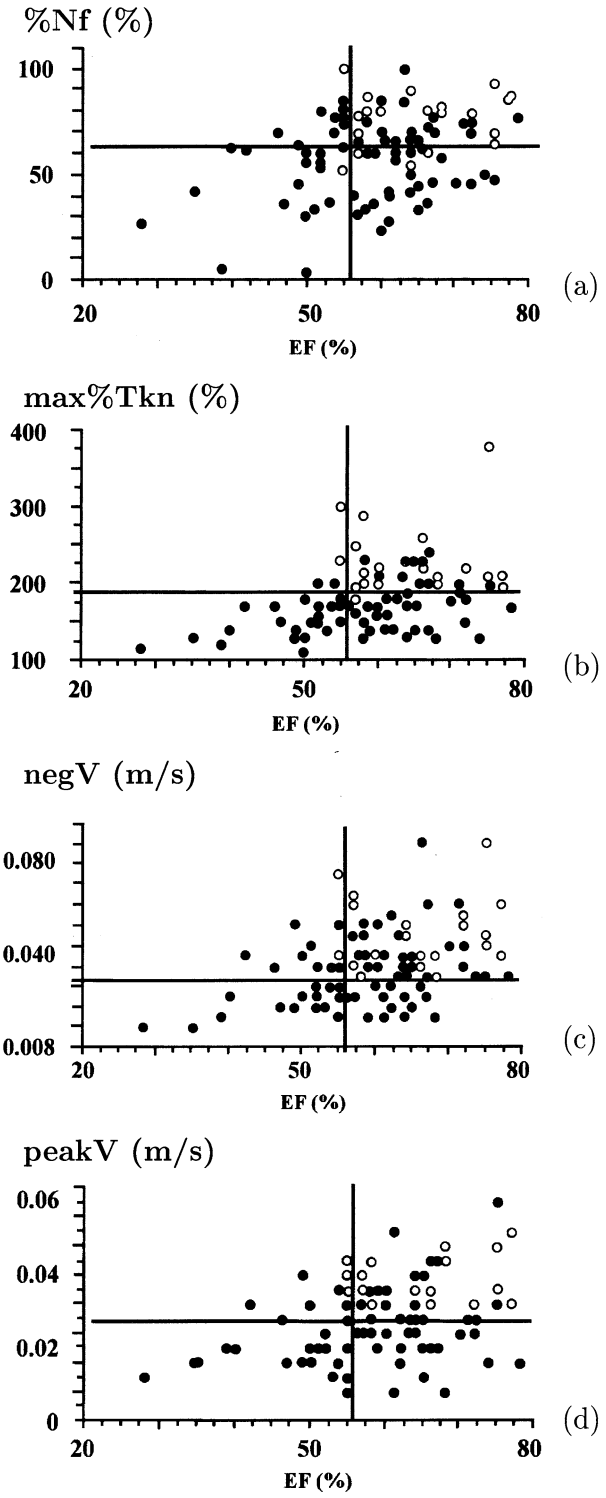

Fig. 3. The relationships between EF and the four parameters (%Nf, max%Tkn, negV, and peakV) of the TSF for the patients with DoxCM (●) and healthy subjects (○). There is a significant relationship between TSF and EF. Solid lines indicate the lower limit of the normal range (mean-SD value). Many patients demonstrated a decrease in the TSF values but still showed normal EF values.

From multiple stepwise regression analysis using all variables listed in the tables, EF, E and negV were shown to correlate significantly with the magnitude of peakV. Also, EF and peakV were selected for negV, and variables of age, HR, LVDd, peakV and #Nf were selected for max%Tkn. However, no terms from the global function were selected for %Nf (wall thickness and max%Tkn were selected variables, but R2 was only 0.22).

The relationship is summarized as follows

PeakV × 250 (m/s) = (−5.13) × (EF × 100%) + 3.69 × E + 0.42 × negV × 250 (m/s) + 2.53, $p < 0.0001$, $R^2 = 0.549$, F-to-remove value from first to third variables; 4.544, 11.967, 47.364

negV × 250 (m/s) = 7.799 × (EF × 100%) + 1.057 × peakV × 250 (m/s) + (−1.346), $p < 0.0001$, $R^2 = 0.471$, F-to-remove value for first and second variables: 4.029, 48.846.

max%Tkn/100 (%) = (−0.009) × age + (−0.006) × HR + (−0.016) × LVDd (mm) + (0.056) × #Nf + (0.041) × peakV × 250 (m/s) + 2.602, $p < 0.0001$, $R^2 = 0.420$, F-to-remove value from first to fifth variables 6.317, 8.974, 5.815, 13.559, 7.852

%Nf/100 (%) = (−0.03) × wall thickness + (0.264) × max%Tkn × 1/100 (%) + 0.396, $p < 0.001$, $R^2 = 0./221$, F=to-remove vaue for first and second variables: 5.644, 12.149

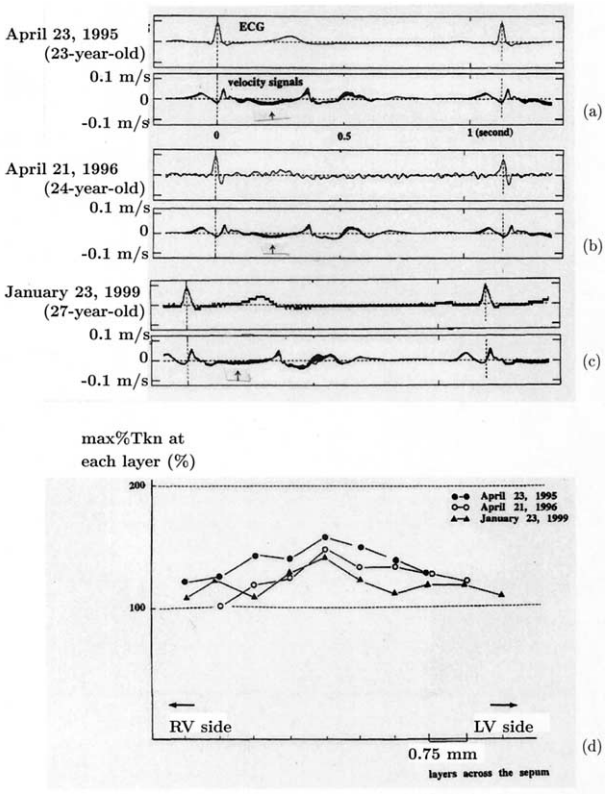

Fig. 4. Top: ECG and superposition of velocity signals at each preset point across the septum from 1995 to 1999 in a 23-year-old male patient, 1995, in stable condition of complete remission. Arrow indicates the peak velocity during systole. Bottom: The change in the profile of max%Tkn at each layer across the septum.

DISCUSSION

Clinical evaluation of myocardial functional deterioration under doxorubicin injection is an essential requirement in the management of patients with hematologic malignancy and a variety of cancers. In particular, early detection at a subclinical phase of myocardial damage is significant because heart failure, after it becomes manifest, irreversibly proceeds to a therapy-resistant stage of failure.

In this study using the phased-tracking method, the existence of physiological transmyocardial heterogeneity in humans was demonstrated and a major part of the systolic thickening was found to be caused by the contribution of the middle and left side of the ventricular wall. That is, the functional importance of the midmyocardial side to the endomyocardial side of the left ventricle during systole was consistent with experimental reports, as summarized in Table 1. The temporal change in this transmural function in healthy subjects during systole has been recently reported by our laboratory (Koiwa et al. 2002).

As shown in Fig. 3, the sequential change of parameters of the TSF in many patients differed from that of the conventional parameters: many patients showed an abnormal TSF even though EF remained normal. Moreover, TSF seemed to be a good indicator of myocardial damage during the clinical course. For example, in the TSF from a patient (a 23-year-old man in 1995, 485 mg/m^2 of BSA) in complete remission, as shown in Fig. 4a, b and c, the velocity during systole (arrow) showed a gradual decrease from 1995 to 1999 and the profile in Fig. 4d also indicates a gradual decrease in the max%Tkn.

However, these changes over 4 years were relatively small in magnitude compared with the changes over 5 months in another patient, who died of DoxCM 5 months after the first measurement, as shown in Fig. 5. Thinning, not thickening, occurred during systole in this case of serious DoxCM. The rapidity of the change was in sharp contrast to that of the patient in stable condition, as demonstrated in Fig. 4. Parameters from conventional routine ECG did not sensitively

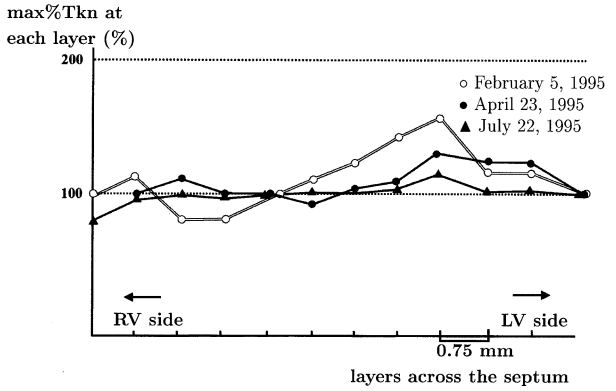

Fig. 5. Superposition of profiles of max%Tkn during 5 months in a patient who died in September 1995 from congestive heart failure. The rapid change in the profile and the appearance of the systolic thinning are in sharp contrast to those of healthy subjects in Fig. 2 and those of the patient in stable condition in Fig. 4.

reflect the change that potentially occurred in the ventricular myocardium (*e.g.*, EF remained within normal limits even 5 months before death in this patient). The possibility of evaluating myocardial damage in a clinical setting using the phased-tracking method is also demonstrated in Fig. 6 for three other patients who died from DoxCM.

The TSFs showed increasing deterioration during their courses, but EF showed fluctuations from normal to abnormal values, probably due to the parameters' preload and afterload dependency. The histological examination of rabbit IVS has confirmed that the myocardial layer function (max%Tkn) shows an inverse linear relationship to the magnitude of the myocardial damage (% of the pathologic lesion that was fibrous and edematous in each area of the myocardial layer) (Koiwa et al. 1998). We speculate that the layer function in the human ventricular wall also reflects, at least in part, the magnitude of the histological deterioration by DoxCM (Bristow et al. 1981), as demonstrated in the animal study.

As shown in Figs. 2 and 3b, when the max%Tkn decreases to less than 200%, we should carefully monitor the patient at an earlier phase of cardiac toxicity, even when the value of EF still remains normal. In particular, the decrease in %Nf or the appearance of transmural systolic thinning should be interpreted as indicative of serious histological and functional deterioration in the myocardium caused by doxorubicin injection. The %Nf is an independent parameter of global function obtained by routine measurement, and %Nf can be evaluated only by this highly sensitive velocity measurement method, that is, the phased-tracking method.

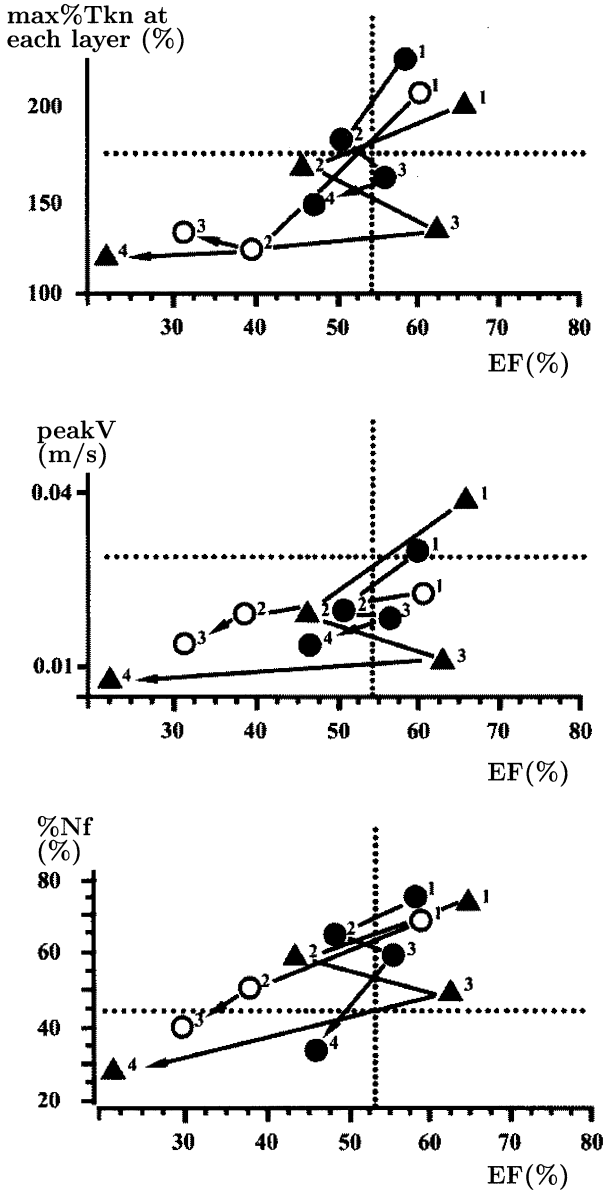

Fig. 6. The sequential change of the three parameters (max%Tkn, peakV, and %Nf, from top to bottom) in the TSF and EF during the clinical course (from 1 to 3 or 4) in three patients that died from DoxCM. In those patients, TSF indicated gradual deterioration during the course, but EF showed significant fluctuation from normal to abnormal.

CONCLUSION

Quantitative information on doxorubicin-induced myocardial damage was obtained by assessing myocardial layer thickening using the phased-tracking method. Information so obtained, therefore, is potentially useful for the rational management of patients with leukemia, malignant lymphoma or other serious diseases requiring treatment with doxorubicin.

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