Importance of Regional Myocardial Layer Function by Phased Tracking Method in Doxorubicin Cardiomyopathy

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Abstract—We examined whether the novel high resolution Doppler technique "the phased tracking method" is useful for evaluating the functional deterioration in doxorubicin cardiomyopathy (DoxCM) following 20 patients of hematological malignancies. In normal subjects, myocardial layer thickening by the phased tracking method occurred homogeneously, i.e., no thinning was observed during systole, across the left ventricular wall. However, in patients, it was characterized by the appearance of non-functioning layers as well as by a decrease in systolic thickening. Conventional echocardiography is not sufficiently sensitive to demonstrate the changes in DoxCM. In contrast, the change in myocardial layer function was useful for showing increasing myocardial deterioration in DoxCM. The phased tracking method supplies useful diagnostic information for DoxCM.

I. BACKGROUND

The quantitative evaluation of the doxorubicin cardiomyopathy (DoxCM) is a serious clinical requisite.[1][2] Recently we have developed the high resolution Doppler method "the phased tracking method" which demonstrates the function at each 0.75mm-thickness myocardial layer across the wall.[3][4] The histological examination of DoxCM in rabbits verified that the layer function by the phased tracking method related closely to the myocardial pathological change.[5] We aimed in this clinical study to clarify whether the measures on each myocardial layer function (MLF) could be a novel diagnostic approach for DoxCM other than conventional approach.

II. METHODS

Subjects

From April 1995 to January 1999, 10 normal subjects (25.7 ± 7.9 year-old, male) and 20 patients of acute leukemia or malignant lymphoma (32.9 ± 11.8 year-old, 12 males and 8 females) were examined for MLF (64 measurements). Among these subjects, four normal volunteers and nine patients were examined repeatedly during the study period and the total number of measurements was sixty-four (normal: 24, patients: 40). Five patients died during the period, two from relapse of the malignancy and three from DoxCM. All Patients received mitoxantrone HCL injection, and the estimated dose of doxorubicine from mitoxantrone HCL was 354.3 ± 154.0mg/m² of body surface area (BSA) as mean ± SD.

Measurements

The following parameters of global function, including ejection fraction (EF) and E/A ratio of the transmitral Doppler velocity were measured by conventional routine echocardiography and pulse Doppler method. The thickness and the instantaneous change of the thickness at each myocardial layer across the interventricular septum of the basal portion in the longitudinal left ventricular B-mode image were measured by the phased tracking method. The basic theory, in vitro, in vivo and clinical evaluations of the myocardial layer thickening rate by this phased tracking method have been detailed previously[3][4] as well as the histological verification using Doxorubicin-injected rabbits.[5]

In practice, a high speed A/D converter with a large-scale memory was employed to analyze the complex signal resulting from the quadrature demodulation of the signal received by a sector type ultrasonic transducer (3.75MHz, and 222µs for repetition interval of the pulses) connected to standard ultrasonic diagnostic equipment. In the diagnostic equipment, the standard longitudinal B-mode cross-sectional image and M-mode image are displayed to identify the measurement points on the left ventricular wall. The resultant real and imaginary signals of the demodulated Doppler signal are 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 were set at peak R in ECG, and spatially set at the right ventricular surface of the septum. The lower limit of the resolution of the change in layer thickness
and the changing rate of the thickness were 0.1μm and 0.1mm/s, respectively.[4]

The following parameters were measured from the myocardial layer thickening: maximum thickening velocity of the layer in the wall (peakV), the profile of %thickening (=systolic thickness/thickness at R-wave) at each layer across the septum, maximum %thickening of the layer across the wall (max%tkn), number of functioning layers at systole showing thickening at the midpoint of the first and second heart sound across the septum (Nf), % of Nf across the wall (%Nf), number of layers showing thickening at diastole of 50ms before QRS of ECG (Dt) and %Dt across the wall.

Statistics

All values are expressed as mean ± SD unless otherwise indicated. ANOVA was used to assess the difference in each variable between normal subjects and patients. When statistically significant results were found, post hoc individual comparison was made with Bonferroni's test. 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, %Nf or %Dt and variables of age, body length, body weight, systolic blood pressure, diastolic blood pressure, HR, LVDd, LVDs, EF, E, E/A and Dose/BSA (P-to-enter value >4.00).

III. RESULTS

Figure 1 shows the myocardial layer thickening in a normal, 26 y-o male (upper panel) and a 22 y-o male patient under doxorubicin treatment (lower panel). From top are ECG, phonocardiogram (PCG), B-mode of the echocardiogram, superposition of loci of tracking lines on the B-mode of the echocardiogram, superposition of velocity signals at each preset points across the septum and the myocardial layer thickening setting right ventricular surface flat. The decrease in the layer’s peak velocity (0.021 ± 0.008m/s vs. 0.034 ± 0.007m/s in normal, P< 0.0001) and the peak thickness (173 ± 32 vs. 223 ± 46% in normal, P< 0.0001) were observed in patients group.

As a whole, The max%tkn ranged 223 ± 46% (300~180%) and no thinning was observed during systole in normal group. In patients at a terminal stage who died of doxorubicin cardiotoxicity thinning, not thickening, occurred during systole. The rapidity of the change in the layer function across the septum was in sharp contrast to those of patients in a stable condition of complete remission.

There are significant relationships between EF and max%tkn or peakV, even the r-value was not so strong (max%tkn=106.3+1.8×EF(%), r=0.42, P<0.01 and peakV(m/s)=0.0083+0.0257×EF(%), r=0.34, P<0.05 thick solid lines in the figure). However, strictly speaking, EF remained within the normal range in many patients despite that peakV or max%tkn showed reduced abnormal value (twelve and sixteen patients respectively).

Fig. 1. The myocardial layer thickening in normal (upper panel, 26 y-o, male) and patient under doxorubicin treatment (lower panel, 22 y-o, male). From top are ECG, phonocardiogram (PCG), B-mode of the echocardiogram, superposition of loci of tracking lines on the B-mode of the echocardiogram, superposition of velocity signals on the preset points across the septum and the myocardial layer thickening setting right ventricular surface flat. See detail in text.

The increase in heterogeneity across the wall were significant in patients (%Nf: 57.3 ± 17.0% vs. 76.9 ± 11.6% in normal, P<0.0001, %Dt: 25.4 ± 21.5% vs. 7.2 ± 10.2% in normal, P<0.01). There was no significant relationships between EF and %Nf or be-
between E/A and %Dt. Equations from the multiple stepwise regression analysis, %Nf and %Dt showed no significant regression when using the variables of basal characteristics and Dose/BSA.

IV. DISCUSSION

One of the major problems of Doxorubicin therapy for malignant neoplasms is that, as has been repeatedly stressed in several reviews and editorials,[1][2] we still have not obtained a sensitive, noninvasive method for diagnosing the subclinical myocardial damage in the daily clinical practice, notwithstanding many efforts adopting exercise echocardiography, radionuclide angiography or Doppler techniques.[6][7][8]

The novel Doppler method reported here is unique in informing us of the functional deterioration of each myocardial layer of 0.75mm-thickness. Histology examination of the interventricular septum in rabbits with 5-week (n=3), 8-week (n=5) and 10-week (n=2) doxorubicin injection (0.53mg/kg, 3days/week), which was performed just after the measurement of the myocardial layer function, confirmed that the myocardial layer function showed an inverse linear relationship to the magnitude of the myocardial damage (% of the pathological lesion that was fibrous and edematous in each area of the myocardial layer). Therefore, we speculated that the layer function in the human ventricular wall in this study reflects mainly the magnitude of the histological deterioration by doxorubicin cardiotoxicity.

Recently, the clinical importance of the functional evaluation of the inner and outer layers of the ventricular wall has strongly been suggested in the study of MR tagging.[9][10] The higher spatial and temporal resolution across the ventricular wall and easier handling for the daily clinical practice to measure the index of the heterogeneity, such as %Nf, %Dt or the profile by the phased tracking method serves further information of the DoxCM other than the measures of the routine method.

One of the important points is that the clinical course of patients is in accordance with the change in the parameter from the layer function, but not with the parameters from the conventional routine echocardiography. That is, when the patient was in a stable condition of complete remission, the profile was also stable. In three patients who died of DoxCM, the profile changed rapidly and systolic thinning was observed. Otherwise EF remained normal even several months before the death. Such discrepancy between the global ventricular function and the regional function was also demonstrated in as 12 of 38 and 16 of 39 cases showed reduced max%tkn and peakV values in spite the fact that they had normal EF value. Moreover, in three patients who died from DoxCM during the study period, MLF showed constantly and increasing deterioration during their courses, but EF showed serious variation from normal to abnormal value during the clinical course in these patients, which resulted in the difficulty to evaluate the increasing risk of severe congestive heart failure for each patient.

We consider at present that measures from the velocity signals (e.g., peakV or max%tkn) would be more useful for early detection of DoxCM than the conventional measures in the daily clinical practice. When the peakV decreases to 2.0>, we should carefully monitor the patient at an earlier phase of cardiac toxicity. In contrast, %Nf or %Dt should be interpreted as an indicator of the existence of significant histological and functional deterioration in the myocardium resulting from the DoxCM.

V. CONCLUSION

The noninvasive measure of each layer's function and its spatial heterogeneity across the wall by "the phased tracking method" could be a requested quantitative evaluation for patients under doxorubicin treatment.

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REFERENCES

