

MONITORING OF THE VERY EARLY CHANGES OF LEFT VENTRICULAR DIASTOLIC FUNCTION IN PATIENTS WITH ACUTE LEUKEMIA TREATED WITH ANTHRACYCLINES

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Aim: To analyze the very early changes of diastolic LV function during and after chemotherapy (CT) in patients with newly diagnosed acute leukemia. **Methods:** 26 patients with acute leukemia have been studied. The cardiac echo evaluation was performed at the baseline (before CT), after the first CT (mean cumulative anthracyclines dose 136.3 ± 28.3 mg m⁻²), after the last CT (mean cumulative anthracyclines dose 464.3 ± 117.5 mg m⁻²) and *circa* 6 months after the completion of CT. **Results:** We found a significant decrease in LVEF ($65.3 \pm 4.5\%$ vs $60.2 \pm 5.7\%$, $p < 0.01$), the fractional shortening of the LV ($34.8 \pm 3.7\%$, vs $29.5 \pm 5.0\%$, $p < 0.01$), but the mitral flow rapid filling velocity (E-wave) was not changed (0.74 ± 0.18 ms⁻¹, vs 0.67 ± 0.17 ms⁻¹, p ns), and atrial filling velocity (A-wave) increased (0.66 ± 0.15 ms⁻¹ vs 0.78 ± 0.18 ms⁻¹, $p < 0.01$). E/A ratio significantly decreased (1.18 ± 0.35 vs 0.89 ± 0.27 , $p < 0.01$). IVRT increased (71.5 ± 11.6 ms vs 84.0 ± 11.6 ms, $p < 0.01$). DT E-wave velocity increased (162.3 ± 25.8 ms vs 206.7 ± 25.5 ms, $p < 0.01$). After the first CT, the signs of LV diastolic dysfunction were detected in 5 (19.2%) patients. 6 months after the last CT, two of these patients (7.7%) developed LV systolic dysfunction with the clinical symptoms of heart failure. Six months after the last CT, 12 (46.2%) patients developed the signs of LV diastolic dysfunction. **Conclusion:** Chemotherapy can induce early changes of diastolic left ventricular function. We consider using Doppler echocardiography as the election tool not only for baseline cardiologic screening but also for the monitoring of the earliest subclinical signs of cardiotoxicity.

Key Words: cardiotoxicity, left ventricular diastolic dysfunction, echocardiography.

In the last decade, chemotherapy (CT) has shown a significant reduction of morbidity and mortality of the hematologic patients. However, the beneficial effects of this therapy can be limited by the development of acute or chronic cardiotoxicity, and the early detection of cardiotoxicity due to CT is a critical issue in the clinical setting [1]. Various methods are recommended to diagnose cardiotoxicity, such as electrocardiography or the evaluation of biochemical markers [2, 3]. In process of time, echocardiography has emerged as the most useful test of the non-invasive detection of cardiotoxicity [4]. Echocardiography allows identifying the early markers of the systolic and diastolic left ventricular (LV) dysfunction. Silent diastolic dysfunction is considered to be the first manifestation of the cardiac related toxicity and is followed by systolic dysfunction [5]. In our pilot study, we have used the serial of Doppler echocardiographic measurements to analyze the very early changes of diastolic LV function during and after CT in patients with newly diagnosed acute leukemia.

Twenty-six consecutive patients (15 males, 11 females, mean age of 46.2 ± 12.4 yrs, range: 22–61 yrs), with acute leukemia have been studied. Seven patients were treated for arterial hypertension. Renal and liver functions were normal in all patients. No patient has been treated with CT or radiotherapy previously. The

patients have been given 2–6 cycles of conventional CT containing anthracycline agent in the total cumulative dose of 464.3 ± 117.5 mg m⁻² (range: 240–715, median 425.5). To calculate the total cumulative dose of anthracyclines, we have applied the conversion factors derived from the maximum recommended cumulative doses for individual agents used (idarubicine, daunorubicine, mitoxantrone). Cardioprotection with dexrazoxane hasn't been used. Afterwards, sixteen patients have undergone the preparative regimen and hematopoietic cell transplantation within two months after the completion of CT. The local ethical committee approved the study protocol. All patients provided a written consent before they were included in the study. The cardiac evaluation was performed at the baseline (before CT), after the first CT (mean cumulative anthracyclines dose 136.3 ± 28.3 mg m⁻²), after the last CT (mean cumulative anthracyclines dose 464.3 ± 117.5 mg m⁻²) and *circa* 6 months after the completion of CT (range: 5–8 months, median 6.0). The ECHO evaluation was performed on Hewlett Packard Image Point machine. The parameters of the systolic and the diastolic LV function and the presence of pericardial effusion were assessed. The systolic LV function was assessed using LV ejection fraction (LVEF) and fractional shortening (FS). To evaluate diastolic LV function, we used the major pulsed-wave Doppler indexes of impaired diastolic function: E/A ratio, E-wave deceleration time (DT) and isovolumic relaxation time of the left ventricle (IVRT). The diastolic LV dysfunction was defined as E/A inversion and DT-E above 220 ms on the transmitral Doppler curve (impaired relaxation).

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Abbreviations used: CT – chemotherapy; DT – deceleration time; EF – ejection fraction; FS – fractional shortening; IVRT – isovolumic relaxation time; LV – left ventricular; LVEF – LV ejection fraction.

Pericardial effusion was defined as the separation of pericardial leaves at least 2 mm in systole. The statistical analysis was performed with the “Statistica for Windows, Version 5.0” program. The analysis of the variance test was used. The values are expressed as mean \pm SD. The probability value (p) $<$ 0.01 was considered statistically significant.

During the six-month follow-up, we found a significant decrease in LVEF ($65.3 \pm 4.5\%$ vs $60.2 \pm 5.7\%$, $p < 0.01$), the fractional shortening of the LV ($34.8 \pm 3.7\%$, vs $29.5 \pm 5.0\%$, $p < 0.01$), but the mitral flow rapid filling velocity (E-wave) was not changed ($0.74 \pm 0.18 \text{ ms}^{-1}$, vs $0.67 \pm 0.17 \text{ ms}^{-1}$, p ns), and atrial filling velocity (A-wave) increased ($0.66 \pm 0.15 \text{ ms}^{-1}$ vs $0.78 \pm 0.18 \text{ ms}^{-1}$, $p < 0.01$). Therefore, E/A ratio significantly decreased (1.18 ± 0.35 vs 0.89 ± 0.27 , $p < 0.01$). IVRT increased ($71.5 \pm 11.6 \text{ ms}$ vs $84.0 \pm 11.6 \text{ ms}$, $p < 0.01$). DT E-wave velocity increased ($162.3 \pm 25.8 \text{ ms}$ vs $206.7 \pm 25.5 \text{ ms}$, $p < 0.01$). During the 6-month follow-up, there were no significant changes in left atrium, right ventricular, left ventricular end-systolic and end-diastolic diameters. After the first CT, the signs of LV diastolic dysfunction were detected in 5 (19.2%) patients. 6 months after the last CT, two of these patients (7.7%) developed LV systolic dysfunction with the clinical symptoms of heart failure. Six months after the last CT, 12 (46.2%) patients developed the signs of LV diastolic dysfunction.

As the anthracycline-induced cardiotoxicity is largely irreversible, it is crucial to detect the myocardial injury at its earliest possible stage [6, 7]. However, the parameters of the systolic function of the left ventricle (EF and FS) are not very sensitive to diagnose the subclinical forms of cardiotoxicity. Therefore, Doppler derived diastolic indexes are recognized as early signs of the left ventricular dysfunction in patients undergoing CT [4].

In our study, we have showed that the first changes in diastolic LV function could develop even in a few weeks after starting of CT. We have found the significant changes of Doppler derived echocardiographic diastolic parameters of the left ventricle — the significant decrease of E/A ratio, prolongation of DT of the E-velocity and IVRT. We have also found the decrease of the systolic LV parameters — EF and FS.

The diagnostic role of Doppler echocardiography to detect cardiotoxicity after anthracycline therapy was studied previously. Krupicka *et al.* [8] investigated possible acute effects in 88 patients with Hodgkin's lymphoma who did not show the significant changes of M-mode derived LV end-diastolic diameter, end-systolic diameter and EF, but identified regional wall motion abnormalities (hypokinesis) by 2D assessment. The chronic cardiotoxicity is often manifested by LV dysfunction and heart failure, which may be detected by the monitoring of Doppler diastolic indexes earlier than by measurement of ejection fraction (EF) [9].

Early peak flow velocity to atrial peak flow velocity (E/A) ratio, deceleration time and isovolumic relaxation time were all impaired (grade I of diastolic dysfunction) in more than 50% of patients treated with anthracyclines, when EF was still normal.

Compared to previous observations [6, 10–12], our study refers very early changes of the diastolic function of the left ventricle in patients undergoing anthracycline chemotherapy. These changes are considered to be the risk factors for development of heart failure in the future and can develop very early after the start of the anthracycline treatment. Motivated by this experience, we consider using Doppler echocardiography as the election tool not only for baseline cardiologic screening but also for the monitoring of the earliest subclinical signs of cardiotoxicity in oncologic patients during and after CT.

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МОНИТОРИНГ РАННЕЙ ДИАСТОЛИЧЕСКОЙ ДИСФУНКЦИИ ЛЕВОГО ЖЕЛУДОЧКА У БОЛЬНЫХ ОСТРОЙ ЛЕЙКЕМИЕЙ, ПРОШЕДШИХ КУРС ЛЕЧЕНИЯ АНТРАЦИКЛИНАМИ

Цель: проанализировать ранние изменения диастолической функции левого желудочка (ЛЖ) во время проведения химиотерапии (ХТ) и после ХТ у больных с первичнодиагностированной острой лейкемией. **Методы:** обследованы 26 больных с острой лейкемией. Эхокардиограммы снимали до ХТ, после первого курса ХТ (среднее значение суммарной дозы антрациклинов $136,3 \pm 28,3$ мг m^{-2}), после окончания ХТ (среднее значение суммарной дозы антрациклинов $464,3 \pm 117,5$ мг m^{-2}) и через 6 мес после завершения ХТ. **Результаты:** выявлено значительное уменьшение фракции выброса ЛВ ($65,3 \pm 4,5\%$ против $60,2 \pm 5,7\%$, $p < 0,01$), фракции укорочения диастолы ЛЖ ($34,8 \pm 3,7\%$ против $29,5 \pm 5,0\%$, $p < 0,01$). Скорость наполнения митрального потока (Е-волна) не изменялась ($0,74 \pm 0,18$ ms^{-1} против $0,67 \pm 0,17$ m s^{-1}), и предсердная скорость наполнения (А-волна) повышалась ($0,66 \pm 0,15$ ms^{-1} против $0,78 \pm 0,18$ ms^{-1} , $p < 0,01$). Отношение Е/А существенно уменьшалось ($1,18 \pm 0,35$ против $0,89 \pm 0,27$, $p < 0,01$). Время изоволюметрического расслабления увеличивалось ($71,5 \pm 11,6$ ms против $84,0 \pm 11,6$ ms , $p < 0,01$). Время замедления кровотока Е-волны увеличивалось ($162,3 \pm 25,8$ ms против $206,7 \pm 25,5$ ms , $p < 0,01$). После первого курса ХТ признаки диастолической дисфункции ЛЖ выявлены у 5 (19,2%) больных. Через 6 мес после окончания ХТ у 2 больных (7,7%) развилась систолическая дисфункция ЛЖ с клиническими симптомами паралича сердца, а у 12 (46,2%) больных выявлены признаки диастолической дисфункции ЛЖ. **Выводы:** ХТ может вызывать ранние изменения диастолической функции ЛЖ. Предлагается использовать эхокардиографию Доплера не только для предварительного скрининга, но и для мониторинга ранних субклинических признаков кардиотоксичности.

Ключевые слова: кардиотоксичность, диастолическая дисфункция левого желудочка, эхокардиография.