Primary Published

J Compr Ped. 2018 August; 9(3):e59701. doi: 10.5812/compreped.59701.

Published online 2018 July 22. **Research Article**

Anthracycline-Induced Cardiothoxicity in Children Cancer Patients: An Imaging Study by Two-Dimensional Global Longitudinal Strain Using Automated Function Imaging Technique

Mohammad Reza Mirzaaghayan [1], Leili Koochakzade [2], Aalie Safari [2], Mohammad Taghi Majnoon [1], Ali-Asghar Zeinaloo [1], Chehreh Mahdavi [1], Azin Ghamari [3], Ehsan Aghaei Moghadam [1,*], Armen Kocharian [1], Farzad Kompani [2] and Maryam Nikoufar [1]

[1] Division of Pediatric Cardiology, Children's Medical Center Tehran University of Medical Sciences, Tehran, Iran
[2] Division of Pediatric Oncology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[3] Tehran University of Medical Sciences, Tehran, Iran

[*] *Corresponding author*: Ehsan Aghaei Moghadam, Division of Pediatric Cardiology, Children's Medical Center, No 62, Dr. Gharib St, Tehran, Iran, E-mail: ehsan_aghaei1358@yahoo.com

Received 2017 August 07; **Revised** 2018 April 08; **Accepted** 2018 April 16.

Abstract

Background: Despite high effectiveness of Anthracycline as a potent antineoplastic agent, its-related cardiothoxicity is the most notorious complication. The purpose of our study was to assess the value of using different methods (LVEF, E, E', A and Tei index versus global longitudinal strain) for detection of early cardiac changes by measuring them before and one month after the Anthracycline administration in a cross-sectional cohort study.

Methods: This cross-sectional study was performed on 22 new diagnosed cancer patients aged 18 years or younger who referred to the children Medical center in Tehran in 2016 as the cases and also 22 age-matched healthy children who referred to the center because of any non-cardiac reasons as the control. All participants were assessed to determine the left ventricular functional indices before and also one month after starting the therapeutic regimen containing Anthracycline.

Results: Among all parameters assessed by echocardiography, only the mitral annular peak systolic velocity (Sm) significantly reduced after administrating Anthracycline compared to before that. Data for patients and the control group showed no statistical significant differences before the therapy as well.

Conclusions: Our findings show that evaluating Sm is most useful for early detection of cardiac changes. This may be due to our limitation of small cohort studies and also the short interval after the drug administration; although this was related to the main goal of our study.

Keywords: Chemotherapy, Echocardiography, Ventricular Function, Strain, Anthracycline

1. Background

It has been estimated that more than 14% of the children who were alive and adults with histories of cancer, were prone to cancer treatment-induced cardio toxicity in USA in 2014 (1). Anthracycline is an important drug for the treatment of pediatric and adult cancers. Despite its high effectiveness, some adverse and even life-threatening drug-induced side effects are potentially concerned. In this regard, cardiothoxicity is the most notorious and well-studied complication (2). The main pathophysiology of symptomatic heart failure is subclinical myocardial cell injury, which leads to an early asymptomatic decrement in the left ventricle ejection fraction (LVEF). This complication has been reported in numerous patients in one year following the Anthracycline treatment completion, however, late LVEF reduction has been revealed in only 2% of them; on the other hand, in about 82% of patients, the recovery from this event was achieved, especially by administrating cardio protective agents such as ACE inhibitors and beta-blockers over a mean period of 3 to 13 months. In this regard, cardiac monitoring of affected patients as well as those symptomatic or even asymptomatic patients under treated with cardio protective drugs is generally acknowledged (3-5). Left ventricular ejection fraction (LVEF) is used for cardiac function monitoring as routine (6), however, it has limited sensitivity (7, 8). It has been demonstrated that despite immediate diagnosis of LVEF decrement following the Anthracycline treatment, 36% could not recover normal EF in spite of therapeutic interventions (9). Some studies have shown that subtle and early changes of LV systolic dysfunction are detectable by myocardial deformation in-

Copyright © 2018, Journal of Comprehensive Pediatrics. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/) which permits copy and redistribute the material just in noncommercial usages, provided the original work is properly cited

Primary Published

dices (strain and strain rate) before LVEF become impaired (10).

This study aims to investigate the value of using different methods (LVEF, E, E', A and Tei index versus global longitudinal strain) for detection of early cardiac changes by measuring them before and one month after the Anthracycline administration in a cross-sectional cohort study.

2. Methods

This cross-sectional study was performed on 22 new diagnosed cancer patients aged 18 years or younger who referred to the children Medical center in Tehran in 2016 as the cases and also 22 age-matched healthy children who referred to the center due to any non-cardiac reasons as the control. The exclusion criteria included lack of consent to participate in research, using anthracycline in previous therapeutic regimen, inappropriate images in echocardiography, history of congenital heart defects, having left ventricular dysfunction of any reason before the start of treatment with anthracycline, and using cardiothoxic drugs before assessment. The baseline characteristics and medical history were collected by interviewing the parents or from the recorded files. All participants were assessed to determine the left ventricular functional indices before and also one month after starting the therapeutic regimen containing anthracycline. Echocardiography was conducted in a lateral decubitus position using a vivid E9 general electric ultrasound machine and a probe 5 seconds in 2, 3, and 4 chamber views. The frame rate was considered similar in both patients and healthy groups. The end of systole was considered as the time of aortic valve closure at apical long axis view. The region of interest was determined manually at the end of systole by determining the endocardial margin at apical and parasternal views. Manual balancing was performed in the presence of inappropriate automated tracking. Segmental and mean strain rates were determined automatically in all acoustic markers (six segments in each view). In total, the global longitudinal strain (averaging all segmental strain rates) was calculated. Diastolic function status was assessed through measurement of E' parameter (early myocardial velocity) in lateral mitral annulus, TDI, and E velocity (early diastolic mitral inflow velocity). Left ventricular ejection fraction was assessed by M mode technique in four chamber views.

The SPSS version 22.0 for windows (SPSS Inc., Chicago, IL) was used for the statistical analysis, and P values of 0.05 or less were considered statistically significant.

3. Results

In total, 4 patients diagnosed with cancer and 7 healthy children were excluded based on the exclusion criteria. In addition, 18 cancer patients who suffered from different types of hematologic cancers and 15 healthy individuals, as the controls, were included into the study. The mean age of participants in the case and control group was 7.55 ± 3.29 years and 5.73 ± 3.16 years respectively with no difference ($P = 0.11$). Also, 61.1% in the case group and 53.3% in control group were male, respectively ($P = 0.65$). Regarding types of cancers, the most common type was acute lymphoblastic leukemia (57.5%) followed by hutchins lymphoma (30%), acute myelocytic lymphoma (6.5%), and Burkitt lymphoma (6%). As shown in Table 1, among all parameters assessed by echocardiography, only the mitral annular peak systolic velocity (Sm) significantly reduced after administrating anthracycline compared to before that, however, the change in other parameters remained statistically insignificant. All echocardiographic data related to the case group after first dose administration of Anthracycline, showed no statistical meaningful differences from those before the therapy, except for Sm. Data for patients and the control group showed no statistical significant differences before the therapy.

4. Discussion

Anthracycline is considered as the main treatment of the hematologic cancers (11-13). Symptomatic heart failure caused by administration of Anthracycline is occurred in 2% - 5% of patients and is more common in hematologic malignancies (14-17). According to these findings we chose children with hematologic malignancies administrated by Anthracycline for the chemotherapy regimen as our study group.

Studies assessing the influence of Anthracycline on myocardial cellular changes in experimental models have demonstrated several forms of cardiac injury leading to myocyte death. The evidences of this cellular damage can be detected by some echocardiographic and laboratory changes such as elevations in serum troponin. In total, development of cellular "sarcopenia" characterized by disruption of normal sarcomere structure is considered as a mechanism of myocyte injury, other than myocyte cell death, which seems to be the probable mechanism for anthracycline-induced cardiac injury (18). When the Anthracycline-induced heart failure becomes symptomatic, the survival will be less than 50% in the following year (19). It has been estimated that death, due to cardiac events, is more probable in childhood cancer survivors compared to normal population with the relative risk of

Table 1. Parameters Assessed by Echocardiography[a]

Variables	Before	After	P Value
E	90.39 ± 17.62	87.61 ± 14.86	0.52
A	59.27 ± 14.73	56.11 ± 13.07	0.28
E'	15.44 ± 3.45	13.83 ± 3.90	0.11
A'	7.67 ± 2.17	7.06 ± 2.41	0.26
Sm	10.72 ± 3.44	8.39 ± 2.89	0.030
LV tei	0.39 ± 0.08	0.39 ± 0.07	0.91
EF	61.72 ± 9.08	57.61 ± 8.44	0.19
FS	32.78 ± 6.82	30.06 ± 5.63	0.23
LV Idd	3.46 ± 0.91	3.72 ± 0.39	0.24
Basal anterior	-17.11 ± 13.07	-13.7 ± 11.83	0.37
Basal anterioseptal	-15.89 ± 7.60	-16.72 ± 3.64	0.69
Basal infroseptal	-17.39 ± 8.73	-17.89 ± 8.33	0.85
Basal inferio	-14.05 ± 14.27	-16.1 ± 12.31	0.64
Basal inferiolateral	-17.97 ± 9.51	-15.31 ± 10.05	0.46
Basal anterolateral	-17.61 ± 11.87	-16.83 ± 8.23	0.81
Mid anterior	-24.67 ± 6.32	-21.67 ± 6.34	0.09
Mid anteroseptal	-22.11 ± 2.65	-21.39 ± 3.43	0.44
Mid infroseptal	-23.06 ± 4.72	-23.11 ± 3.19	0.96
Mid inferior	-20 ± 10.21	-17.72 ± 10.73	0.35
Mid inferolateral	-20.61 ± 8.04	-21.33 ± 6.08	0.72
Mid anterolateral	-22.44 ± 8.36	-22.09 ± 4.05	0.85
Apical anterior	-27.77 ± 4.68	-26.5 ± 4.19	0.38
Apical seotal	-27.28 ± 4.67	-25.94 ± 4.04	0.42
Apical inferior	-27.56 ± 5.04	-24.79 ± 5.82	0.12
Lateral	-28.28 ± 5.45	-25.72 ± 5.13	0.08
Apex	-28.39 ± 4.38	-26.22 ± 3.78	0.11
GLP average	-22.45 ± 3.15	-21.07 ± 2.72	0.17
HR	113.11 ± 20.45	110.39 ± 15.16	0.66

[a]Values are expressed as mean ± SD.

8.2 (7). Regarding the high mortality of heart failure caused by Anthracycline, early detection of cardiac changes and using preventable therapeutic strategies for decelerating this process becomes much more important.

Potential risk factors for Anthracycline-induced cardiac damages are: female sex, earlier age at the time of treatment, higher body fat content, concurrent radiation therapy, and higher cumulative dose of Anthracycline (20, 21).

Evaluation of left ventricular ejection fraction (LVEF), fractional shortening (FS), E' parameter (early diastolic velocity), E parameter (trans mitral early diastolic filling velocity), A parameter (trans mitral late diastolic filling velocity) and mitral annular peak systolic velocity (Sm) by 2 dimensional (2D), and M-mode echocardiography, are the conventional methods for cardiac changes assessment. Recently, utilizing of cardiac strain and strain rate, for regional and global systolic dysfunction evaluation, has been considered. Studies suggest that LVEF and FS lack enough sensitivity for early cardiac changes detection (7, 8). On the other hand, recent studies show that cardiac strain decreases in both early and late cardiac changes caused by Anthracycline (22, 23). Some studies have shown that subtle and early changes of LV systolic dysfunction are detectable by myocardial deformation indices (strain and strain rate) before LVEF decreases (10, 24). Comparing the conventional methods with recent ones, our study aimed to determine the relative efficiency of these indices.

In a study done by Ali et al., 6% of treated patients suffered from cardiac adverse events after the use of anthracyclines that manifested by lowering LVEF and GLS (25). In a similar study by Pignatelli et al., abnormal global longitudinal peak systolic strain was detected in 60% of patients and 76% had abnormal peak circumferential strain compared to age-matched controls (26). As indicated by Corapcioglu et al., 48% of the patients had cardiac dysfunction following the anthracycline chemotherapy. Found by echocardiography, all dysfunctions were systolic, whereas 29% of the patients had diastolic and 38% of the patients had systolic dysfunction in a study by multigated radionuclide angiography (27). In another study by Ishii et al., the patients who received a low dose and those who received a moderate to high dose of Anthracycline had a significant difference in the Tei index (28). In another study by Agha et al., the LV developed a change in its longitudinal systolic function in the form of a reduction in MAPSE, TDI-derived systolic velocity of lateral mitral annulus, 2D-STE-derived global longitudinal strain, and 2D-STE-derived global longitudinal strain rate, following the chemotherapy (29).

Children affected by different types of cancer may experience significant adverse changes in the left ventricular functional and also structural parameters. These changes can be manifested by reducing the left ventricular ejection fraction, increasing left ventricular Tei index, and also impaired segmental wall motion as impaired left ventricular strain. As mentioned above, it is crucial to detect the early stages of the Anthracycline-induced cardiac changes. Our aim was to determine the immediate effect of the Anthracycline on cardiac function by using conventional and newer methods of echocardiography. Based on our findings, only the mitral annular peak systolic velocity (Sm) was significantly reduced after administrating Anthracycline and the changes in other parameters, including global longitudinal strain and global longitudinal strain rate, remained statistically insignificant. Our find-

Primary Published

ings show that evaluating Sm is most useful for early detection of cardiac changes and recent indices have no privilege compared to more conventional ones. This may be due to our limitation of small cohort studies and also the short interval after the drug administration, although, this was related to the main goal of our study.

References

1. National Cancer Insitute NIoH , DHHS , Bethesda MD. *Cancer Trends Progress Report*. 2011/2012.
2. Middleman E, Luce J, Frei E. Clinical trials with adriamycin. *Cancer*. 1971;**28**(4):844–50. doi: 10.1002/1097-0142(1971)28:4<844::aid-cncr2820280407>3.0.co;2-9.
3. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2012;**23 Suppl 7**:vii155–66. doi: 10.1093/annonc/mds293. [PubMed: 22997448].
4. Giantris A, Abdurrahman L, Hinkle A, Asselin B, Lipshultz SE. Anthracycline-induced cardiotoxicity in children and young adults. *Crit Rev Oncol Hematol*. 1998;**27**(1):53–68. doi: 10.1016/S1040-8428(97)10007-5. [PubMed: 9548017].
5. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol*. 2009;**53**(15):e1–e90. doi: 10.1016/j.jacc.2008.11.013. [PubMed: 19358937].
6. Romond EH, Jeong JH, Rastogi P, Swain SM, Geyer CE Jr, Ewer MS, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2012;**30**(31):3792–9. doi: 10.1200/JCO.2011.40.0010. [PubMed: 22987084]. [PubMed Central: PMC3478574].
7. Cramer L, Hildebrandt B, Kung T, Wichmann K, Springer J, Doehner W, et al. Cardiovascular function and predictors of exercise capacity in patients with colorectal cancer. *J Am Coll Cardiol*. 2014;**64**(13):1310–9. doi: 10.1016/j.jacc.2014.07.948. [PubMed: 25257631].
8. Ganame J, Claus P, Uyttebroeck A, Renard M, D'Hooge J, Bijnens B, et al. Myocardial dysfunction late after low-dose anthracycline treatment in asymptomatic pediatric patients. *J Am Soc Echocardiogr*. 2007;**20**(12):1351–8. doi: 10.1016/j.echo.2007.04.007. [PubMed: 17604960].
9. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*. 2010;**55**(3):213–20. doi: 10.1016/j.jacc.2009.03.095. [PubMed: 20117401].
10. Yu CM, Sanderson JE, Marwick TH, Oh JK. Tissue Doppler imaging a new prognosticator for cardiovascular diseases. *J Am Coll Cardiol*. 2007;**49**(19):1903–14. doi: 10.1016/j.jacc.2007.01.078. [PubMed: 17498573].
11. Sanz MA, Martin G, Rayon C, Esteve J, Gonzalez M, Diaz-Mediavilla J, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group. *Blood*. 1999;**94**(9):3015–21. [PubMed: 10556184].
12. Tallman MS, Nabhan C, Feusner JH, Rowe JM. Acute promyelocytic leukemia: evolving therapeutic strategies. *Blood*. 2002;**99**(3):759–67. [PubMed: 11806975].
13. Barrett-Lee PJ, Dixon JM, Farrell C, Jones A, Leonard R, Murray N, et al. Expert opinion on the use of anthracyclines in patients with advanced breast cancer at cardiac risk. *Ann Oncol*. 2009;**20**(5):816–27. doi: 10.1093/annonc/mdn728. [PubMed: 19153118].
14. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer*. 2010;**10**:337. doi: 10.1186/1471-2407-10-337. [PubMed: 20587042]. [PubMed Central: PMC2907344].
15. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med*. 1979;**91**(5):710–7. doi: 10.7326/0003-4819-91-5-710. [PubMed: 496103].
16. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*. 2003;**97**(11):2869–79. doi: 10.1002/cncr.11407. [PubMed: 12767102].
17. Limat S, Demesmay K, Voillat L, Bernard Y, Deconinck E, Brion A, et al. Early cardiotoxicity of the CHOP regimen in aggressive non-Hodgkin's lymphoma. *Ann Oncol*. 2003;**14**(2):277–81. doi: 10.1093/annonc/mdg070. [PubMed: 12562656].
18. Sawyer DB, Peng X, Chen B, Pentassuglia L, Lim CC. Mechanisms of anthracycline cardiac injury: can we identify strategies for cardioprotection? *Prog Cardiovasc Dis*. 2010;**53**(2):105–13. doi: 10.1016/j.pcad.2010.06.007. [PubMed: 20728697]. [PubMed Central: PMC2933091].
19. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*. 2000;**342**(15):1077–84. doi: 10.1056/NEJM200004133421502. [PubMed: 10760308].
20. Rodvold KA, Rushing DA, Tewksbury DA. Doxorubicin clearance in the obese. *J Clin Oncol*. 1988;**6**(8):1321–7. doi: 10.1200/JCO.1988.6.8.1321. [PubMed: 3411343].
21. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging*. 2012;**5**(5):596–603. doi: 10.1161/CIRCIMAGING.112.973321. [PubMed: 22744937]. [PubMed Central: PMC3703313].
22. Harake D, Franco VI, Henkel JM, Miller TL, Lipshultz SE. Cardiotoxicity in childhood cancer survivors: strategies for prevention and management. *Future Cardiol*. 2012;**8**(4):647–70. doi: 10.2217/fca.12.44. [PubMed: 22871201]. [PubMed Central: PMC3870660].
23. Hoffmann R, von Bardeleben S, ten Cate F, Borges AC, Kasprzak J, Firschke C, et al. Assessment of systolic left ventricular function: a multi-centre comparison of cineventriculography, cardiac magnetic resonance imaging, unenhanced and contrast-enhanced echocardiography. *Eur Heart J*. 2005;**26**(6):607–16. doi: 10.1093/eurheartj/ehi083. [PubMed: 15618026].
24. Florescu M, Magda LS, Enescu OA, Jinga D, Vinereanu D. Early detection of epirubicin-induced cardiotoxicity in patients with breast cancer. *J Am Soc Echocardiogr*. 2014;**27**(1):83–92. doi: 10.1016/j.echo.2013.10.008. [PubMed: 24268372].
25. Ali MT, Yucel E, Bouras S, Wang L, Fei HW, Halpern EF, et al. Myocardial strain is associated with adverse clinical cardiac events in patients treated with anthracyclines. *J Am Soc Echocardiogr*. 2016;**29**(6):522–7 e3. doi: 10.1016/j.echo.2016.02.018. [PubMed: 27068546].
26. Pignatelli RH, Ghazi P, Reddy SC, Thompson P, Cui Q, Castro J, et al. Abnormal myocardial strain indices in children receiving anthracycline chemotherapy. *Pediatr Cardiol*. 2015;**36**(8):1610–6. doi: 10.1007/s00246-015-1203-8. [PubMed: 26049414].
27. Corapcioglu F, Sarper N, Berk F, Sahin T, Zengin E, Demir H. Evaluation of anthracycline-induced early left ventricular dysfunction

Primary Published

in children with cancer: a comparative study with echocardiography and multigated radionuclide angiography. *Pediatr Hematol Oncol*. 2006;**23**(1):71–80. doi: 10.1080/08880010500313603. [PubMed: 16326416].

28. Ishii M, Tsutsumi T, Himeno W, Eto G, Furui J, Hashino K, et al. Sequential evaluation of left ventricular myocardial performance in children after anthracycline therapy. *Am J Cardiol*. 2000;**86**(11):1279–81. A9. [PubMed: 11090811].
29. Agha H, Shalaby L, Attia W, Abdelmohsen G, Aziz OA, Rahman MY. Early ventricular dysfunction after anthracycline chemotherapy in children. *Pediatr Cardiol*. 2016;**37**(3):537–44. doi: 10.1007/s00246-015-1311-5. [PubMed: 26667956].