Original Article

Vascular Dysfunction in Breast Cancer Patients Receiving Anthracycline Chemotherapy: A Cross-Sectional Study

Siripanya S, MSc[1], Parinyanitikul N, MD[2], Tanaka H, PhD[3], Suksom D, PhD[1,4]

[1] Faculty of Sports Science, Chulalongkorn University, Bangkok, Thailand

[2] Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

[3] Department of Kinesiology and Health Education, The University of Texas at Austin, Austin, TX, USA

[4] Exercise Physiology in Special Population Research Group, Chulalongkorn University, Bangkok, Thailand

Background: Anthracycline has been commonly used in first-line chemotherapy in breast cancer. Little is known about the early vascular changes in the course of anthracycline chemotherapy in patients with breast cancer.

Objective: To determine whether vascular complications could occur shortly after anthracycline chemotherapy treatment in patients with breast cancer.

Materials and Methods: Twenty-nine middle-aged female participants, including healthy controls (CON; n = 10), breast cancer patients who had not received any chemotherapy treatment (BC; n = 9), and breast cancer patients undergoing the anthracycline chemotherapy (BC+AC; n = 10), were studied. Carotid artery intima-media thickness (IMT) and flow-mediated dilation (FMD), an index of endothelium-dependent vasodilation, were measured using the ultrasound machine. Brachial-ankle pulse wave velocity (baPWV) was measured as an index of arterial stiffness using a non-invasive vascular screening device.

Results: There were no significant group differences in age, height, body weight, body mass index, body fat, resting heart rate, blood pressure, maximal oxygen consumption, and the amount of physical activity. FMD was lower while IMT and baPWV were greater in the BC+AC group than in the CON and BC groups (all $p<0.05$). FMD was negatively associated with baPWV ($r=-0.42$, $p=0.02$) and IMT ($r=-0.51$, $p=0.01$). IMT was positively associated with baPWV ($r=0.42$, $p=0.02$).

Conclusion: Patients received anthracycline chemotherapy showed reduced vascular functions within two to three months of exposure to the treatment. These unfavorable changes can be considered not only as risk factors but also as earliest sub-clinical markers.

Keywords: Flow-mediated dilatation, Intima-media thickness, Arterial stiffness, Endothelial dysfunction

J Med Assoc Thai 2019;102(5):554-9
Website: http://www.jmatonline.com
Recieved 16 Nov 2018 | Revised 5 Feb 2019 | Accepted 12 Feb 2019

Breast cancer is the most common cancer among women with over one million new cases diagnosed annually worldwide[1]. The population of cancer survivors has gradually increased in recent decades. However, the cancer survivors are at risk for conditions related to its treatments. Anthracycline chemotherapeutic agents have been commonly used as the first-line chemotherapy in breast cancer[2].

Correspondence to:

Suksom D.

Faculty of Sports Science, Chulalongkorn University, Rama I Road, Pathumwan, Bangkok 10330, Thailand.

Phone: +66-81-3415736, **Fax**: +66-2-2181035

Email: daroonwanc@hotmail.com

The use of anthracyclines is associated with an increased risk of cardiovascular toxicity, including left ventricular systolic dysfunction, cardiomyopathy, and heart failure[3]. Long-term survivors of childhood cancer who were exposed to anthracycline treatment exhibit a marked pre-clinical vascular dysfunction and elevated aortic stiffness[4] as well as increased carotid wall thickness[5]. Even at 10 months following anthracycline-based chemotherapy, brachial artery endothelium-dependent vasodilation appears to be reduced in pediatric cancer patients[6].

Although there has been focus on vascular complications of anthracycline chemotherapy, little is known about the early changes in vascular function in the course of anthracycline chemotherapy in patients

How to cite this article: Siripanya S, Parinyanitikul N, Tanaka H, Suksom D. Vascular Dysfunction in Breast Cancer Patients Receiving Anthracycline Chemotherapy: A Cross-Sectional Study. J Med Assoc Thai 2019;102:554-9.

with breast cancer. Accordingly, the primary purpose of the present pilot study was to determine vascular functions in patients with breast cancers who received the second/third cycles of anthracycline chemotherapy (two to three months of exposure to anthracycline) compared with non-treatment breast cancer patients and healthy women. We hypothesized that vascular dysfunction can occur shortly after anthracycline chemotherapy treatment in patients with breast cancer.

Materials and Methods

Participants

Twenty-nine female subjects aged 40 to 55 years, included healthy controls (CON; n = 10), breast cancer patients who had not received any chemotherapy treatment after operation (BC; n = 9), and breast cancer patients undergoing the second and third cycle from four cycles of anthracycline chemotherapy (BC+AC; n = 10) were studied. The purposive sampling was used for selecting participants. Participants who had a history of cardiovascular disease, respiratory disease, smoking, and alcohol drinking were excluded from the study. Before participation, all of the subjects provided written informed consents. The breast cancer patients were approved by an oncologist and were recruited from the oncology unit, King Memorial Chulalongkorn Hospital between November 2015 and October 2016. Health status was evaluated through a questionnaire. The study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University, COA No.441/2015.

Measurements

Subjects refrained from vigorous physical activity, caffeinated beverages, or alcohol at least 12 hours before the test. All participants underwent a single examination at the same time in the morning. The laboratory experiments were performed in a controlled environment with an ambient temperature of 25°C. Body fat was evaluated using body composition analyzer (Whole Body Bioelectrical Impedance Analysis, ioi 353, JAWON, Korea). Blood pressure and heart rate at rest were measured with semi-automated blood pressure device (CARESCAPE V100, GE Dinamap, USA). Maximal oxygen consumption was estimated from heart rate measured during submaximal exercise test (RS800CX, Polar Electro Oy, FI-90440 KEMPELE, Finland). The Global Physical Activity Questionnaire was used to assess physical activity[7].

Flow-mediated dilation (FMD) was measured as an index of endothelium-dependent vasodilation using blood occlusion technique on the forearm. The brachial artery was imaged above the antecubital fossa in the longitudinal plane with the ultrasound machine (CX50, Philips, Andover, MA). Arterial distension was measured using a computer software program (Brachial Analyzer, Medical imaging applications, Coralville, IA). Brachial artery blood flow was measured with duplex ultrasound and was analyzed manually by using software integral to the ultrasound machine. Vascular resistance was calculated as the ratio of mean arterial pressure to forearm blood flow (ml/minute)[8]. Carotid artery intima-media thickness (IMT) was measured from images derived from an ultrasound machine equipped. Ultrasound images were analyzed by use of computerized software (Carotid Analyzer, Medical imaging applications)[9]. Brachial-ankle pulse wave velocity (baPWV) was measured using a non-invasive vascular screening device (Omron VP-1000, Kyoto, Japan). Pulse wave velocity was calculated from the distance between two arterial recording sites divided by transit time[10].

Statistical analysis

Statistical analysis was performed using the SPSS software package (SPSS, Chicago, USA). Prior to the statistical analyses, tests for normality were conducted using a Shapiro-Wilk test. One-way analysis of variance was used for comparisons among groups. Because body fat and vascular resistance were not normally distributed, the data were analyzed using Kruskal-Wallis tests. Post hoc testing was performed with LSD test if data were normally distributed and the Mann-Whitney U test if data were not normally distributed.

Results

Selected characteristic of the participants are shown in Table 1. There were no significant group differences in age, height, body weight, body mass index (BMI), body fat, heart rate at rest, blood pressure, VO_2 max, and the amount of physical activity. Most of participants with breast cancer exhibited stage IIa breast cancer. The BC+AC group had the cumulative dose of doxorubicin equal 279.6±7.0 mg/m².

FMD was lower and carotid artery IMT and baPWV were greater in the BC+AC group when compare with the CON and BC groups (all $p<0.05$). There was no difference in shear rate at rest, vascular resistance, and vascular conductance between the three groups (Figure 1).

As shown in Figure 2, FMD was negatively associated with baPWV ($r=-0.42$, $p=0.02$) and IMT

Table 1. Selected characteristic of healthy controls (CON), breast cancer patients (BC), and breast cancer patients undergoing anthracycline chemotherapy (BC+AC) groups

Parameters	CON (n = 10) Mean±SD	BC (n = 9) Mean±SD	BC+AC (n = 10) Mean±SD	p-value
Age (years)	41.8±8.0	41.4±7.8	44.2±9.6	0.74
Body weight (kg)	59.1±9.3	55.7±9.4	61.8±12.8	0.47
Height (cm)	157±5	156±5.5	155±4.7	0.86
Body mass index (kg/m^2)	24.0±3.8	23.0±4.0	25.6±4.8	0.41
Body fat (%)	29±5	28±7	32±8	0.26
Heart rate (bpm)	75±7	75±7	82±11	0.11
Systolic blood pressure (mmHg)	110±16	114±19	113±17	0.87
Diastolic blood pressure (mmHg)	72±11	74±9	75±11	0.84
Predicted VO_2 max (ml/kg/minute)	27.6±3.7	25.4±4.0	24.6±5.5	0.32
Physical activity (MET-minutes/week)	1,672±582	1,671±729	1,008±805	0.53
Comorbidity, n (%)				-
None	9 (90)	7 (78)	7 (70)	
Hypertension	0 (0)	1 (11)	0 (0)	
Diabetes mellitus	0 (0)	0 (0)	0 (0)	
Dyslipidemia	0 (0)	1 (11)	2 (20)	
Other	1 (10)	0 (0)	1 (10)	
Side of breast cancer, n (%)				-
Right side	-	6 (67)	3 (30)	
Left side	-	3 (33)	7 (70)	
Bilateral side	-	0 (0)	0 (0)	
Staging, n (%)				-
I	-	1 (11)	1 (10)	
IIA	-	4 (44)	5 (50)	
IIB	-	3 (33)	3 (30)	
IIIA	-	1 (11)	1 (10)	
IIIB	-	0 (0)	0 (0)	
IIIC	-	0 (0)	0 (0)	
IV	-	0 (0)	0 (0)	
Cumulative dose of doxorubicin (mg/m^2)	0	0	279.60±7.02	-

SD=standard deviation

(r=–0.51, p=0.01). IMT was positively associated with baPWV (r=0.42, p=0.02).

Discussion

The main findings of the present cross-sectional study are that patients with breast cancer did not display vascular dysfunction but patients who received anthracycline chemotherapy showed reduced vascular functions within two to three months of exposure to the drug treatment.

The results shown that there were no significant group differences in age, height, body weight, BMI, body fat, resting heart rate, blood pressure, maximal oxygen consumption, and the amount of physical activity. Moreover, there were no differences in any of the vascular function measures between healthy

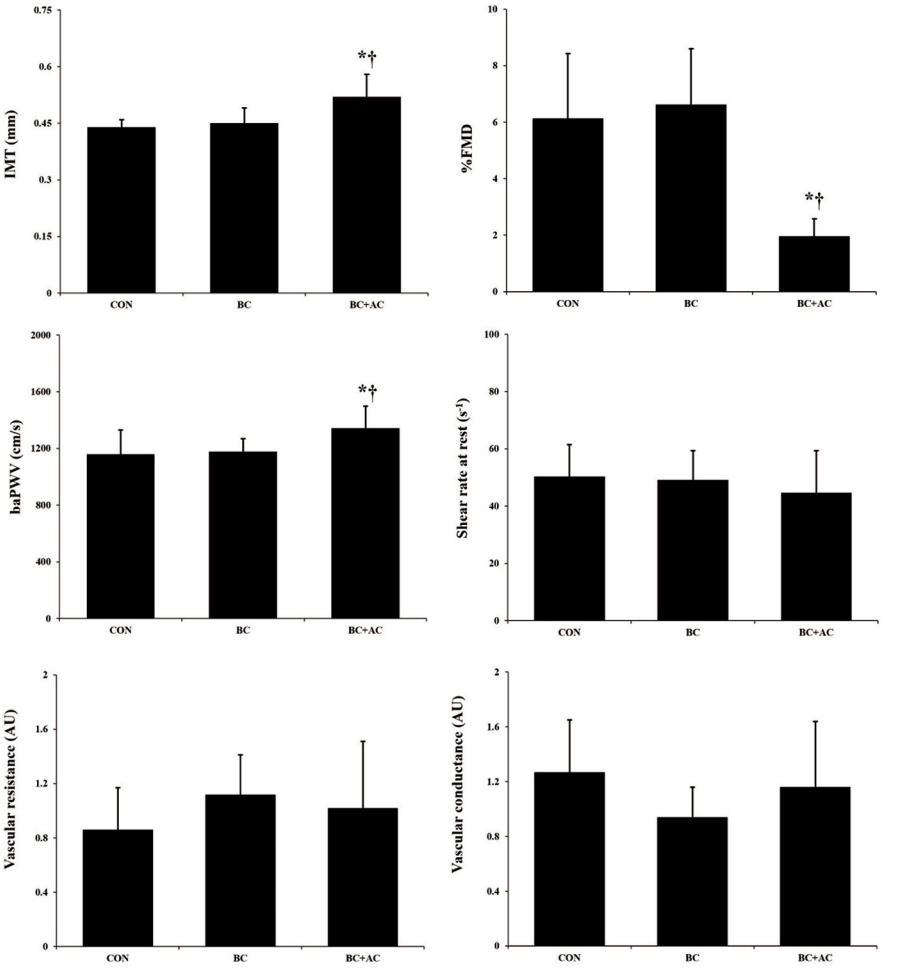

Figure 1. Comparison of vascular parameters in the healthy controls (CON), breast cancer patients (BC), and breast cancer patients undergoing anthracycline chemotherapy (BC+AC) groups.

IMT=intima-media thickness, FMD=flow-mediated dilation, baPWV=brachial-ankle pulse wave velocity

Data expressed as mean±SD, * $p<0.05$ vs. CON, † $p<0.05$ vs. BC

controls and breast cancer patients who did not receive any chemotherapy. However, breast cancer patients who received anthracyclines for two to three months demonstrated vascular dysfunction as assessed by arterial stiffness, endothelium-dependent vasodilation, and arterial wall thickness. The present results are consistent with previous studies showing that the anthracycline-treated group had a significantly lower FMD than the healthy control group[4]. A significant increase in pulse wave velocity has also been reported at six months after administration of low to moderate doses of anthracycline-based chemotherapy[11]. The present study findings provide preliminary evidence that anthracyclines may cause changes in vascular structure and function much earlier than previously thought.

The pathophysiology of chemotherapy-induced impairments in vascular function are not yet fully understood but have been attributed to the effects of anticancer agents on the structural and functional properties of the endothelium. The cytotoxic effects on the endothelium can be a result of a direct effect on endothelial cell activation. Endothelial cell activation is associated with adhesion of inflammatory cells and endothelial cell damage[12]. In vitro and in vivo studies have shown that anthracyclines cause apoptosis of vascular endothelial cells[13]. Additionally, the inhibition of endothelial nitric oxide synthase (eNOS) due to the action of anthracyclines binding to the reductase domain of eNOS has been reported[14].

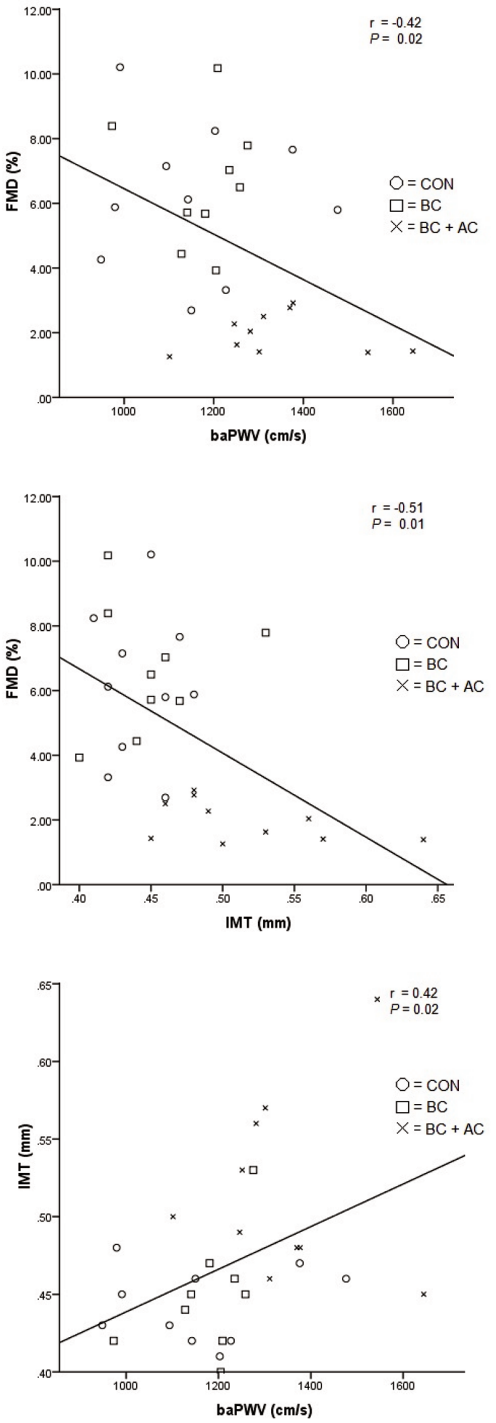

Figure 2. Correlations between carotid artery intima-media thickness (IMT), brachial-ankle pulse wave velocity (PWV), and flow-mediated dilation (FMD) in the healthy (CON), breast cancer patients (BC), and breast cancer patients undergoing anthracycline chemotherapy (BC+AC) groups.

r=correlation coefficient, P=probability value

This could result in a reduction in nitric oxide (NO) production and an increase in superoxide generation and reactive oxygen species (ROS) production. Initiation of oxidative stress through generation of ROS is thought to lead to endothelial dysfunction by enhancing the degradation and inhibiting the synthesis of nitric oxide[15].

There are several limitations in the present study that should be emphasized. First, participants with breast cancer who were undergoing anthracyclines treatment tended to be slightly older and more overweight than the healthy controls and breast cancer patients groups. This may have affected vascular functions independent of anthracyclines. Second, the number of participants studied was relatively small, and the results should be interpreted with caution. Finally, the blood chemical data, i.e., glucose, lipid profile and inflammatory markers were not determined. Therefore, future studies that account for all the limitations described above are warranted.

Conclusion

Anthracycline vascular toxicity can occur acutely within two to three months of initial anthracycline exposure. These unfavorable changes can be considered not only as risk factors but also as earliest sub-clinical markers.

What is already known on this topic?

The use of anthracyclines is associated with an increased risk of cardiovascular toxicity. While long-term anthracycline treatment exhibits vascular dysfunction, the early changes in vascular function in the course of anthracycline chemotherapy in patients with breast cancer is not known.

What this study adds?

The present study indicated that anthracycline vascular toxicity can occur quickly within a few weeks of initial anthracycline exposure. These unfavorable changes can be considered as earliest risk factors of cardiovascular disease and need to be considered.

Acknowledgement

The present study was supported by the Government Research Budget Chulalongkorn University 2016, the 100th Anniversary of Chulalongkorn University and the Ratchadaphiseksomphot Endowment Fund, Chulalongkorn University. Some part of the data had been presented as a poster at the American College of Sports Medicine, 64th Annual Meeting, May 30 to

June 3, 2017 Colorado, Denver, USA.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-386.
2. Biganzoli L, Cufer T, Bruning P, Coleman R, Duchateau L, Calvert AH, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. J Clin Oncol 2002;20:3114-21.
3. Putt M, Hahn VS, Januzzi JL, Sawaya H, Sebag IA, Plana JC, et al. Longitudinal changes in multiple biomarkers are associated with cardiotoxicity in breast cancer patients treated with doxorubicin, taxanes, and trastuzumab. Clin Chem 2015;61:1164-72.
4. Jenei Z, Bárdi E, Magyar MT, Horváth A, Paragh G, Kiss C. Anthracycline causes impaired vascular endothelial function and aortic stiffness in long term survivors of childhood cancer. Pathol Oncol Res 2013;19:375-83.
5. Okur A, Karadeniz C, Özhan Oktar S, Pınarlı FG, Aral A, Oğuz A. Assessment of brachial artery reactivity, carotid intima-media thickness, and adhesion molecules in pediatric solid tumor patients treated with anthracyclines. Pediatr Hematol Oncol 2016;33:178-85.
6. Chow AY, Chin C, Dahl G, Rosenthal DN. Anthracyclines cause endothelial injury in pediatric cancer patients: a pilot study. J Clin Oncol 2006;24: 925-8.
7. Herrmann SD, Heumann KJ, Der Ananian CA, Ainsworth BE. Validity and reliability of the global physical activity questionnaire (GPAQ). Meas Phys Educ Exerc Sci 2013;17:221-35.
8. Dhindsa M, Sommerlad SM, DeVan AE, Barnes JN, Sugawara J, Ley O, et al. Interrelationships among noninvasive measures of postischemic macro- and microvascular reactivity. J Appl Physiol 2008;105: 427-32.
9. Chuensiri N, Tanaka H, Suksom D. The acute effects of supramaximal high-intensity intermittent exercise on vascular function in lean vs. obese prepubescent boys. Pediatr Exerc Sci 2015;27:503-9.
10. Jaruchart T, Suwanwela NC, Tanaka H, Suksom D. Arterial stiffness is associated with age-related differences in cerebrovascular conductance. Exp Gerontol 2016;73:59-64.
11. Drafts BC, Twomley KM, D'Agostino R Jr, Lawrence J, Avis N, Ellis LR, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. JACC Cardiovasc Imaging 2013;6:877-85.
12. Svilaas T, Lefrandt JD, Gietema JA, Kamphuisen PW. Long-term arterial complications of chemotherapy in patients with cancer. Thromb Res 2016;140 Suppl 1: S109-18.
13. Wu S, Ko YS, Teng MS, Ko YL, Hsu LA, Hsueh C, et al. Adriamycin-induced cardiomyocyte and endothelial cell apoptosis: in vitro and in vivo studies. J Mol Cell Cardiol 2002;34:1595-607.
14. Vásquez-Vivar J, Martasek P, Hogg N, Masters BS, Pritchard KA Jr, Kalyanaraman B. Endothelial nitric oxide synthase-dependent superoxide generation from adriamycin. Biochemistry 1997;36:11293-7.
15. Tousoulis D, Davies G, Toutouzas P. Vitamin C increases nitric oxide availability in coronary atherosclerosis. Ann Intern Med 1999;131:156-7.
16. Vapaatalo H, Mervaala E. Clinically important factors influencing endothelial function. Med Sci Monit 2001;7:1075-85.
17. Hadi HA, Carr CS, Al Suwaidi J. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. Vasc Health Risk Manag 2005;1:183-98.