Changes in ischemia-modified albumin in myocardial toxicity induced by anthracycline and docetaxel chemotherapy

Xiao-Dong Luan, Master of Medicinea, Kai-Hua Zhao, Master of Medicinea, Hong Hou, Master of Medicinea, Yan-Hong Gai, Master of Medicineb,c, Qi-Tang Wang, Bachelor of Medicinea, Qiang Mu, Master of Medicinea, Yue Wan, Master of Medicinea

Abstract
This study aimed to evaluate differences in myocardial toxicity induced by different chemotherapy regimens. Patients were divided into 2 groups: epirubicin (EPI) combined with cyclophosphamide (EC) group and docetaxel combined with cyclophosphamide (TC) group. Changes in electrocardiograph (ECG) and ischemia-modified albumin (IMA) were determined pre- and 1, 3, and 6 courses of postchemotherapy. After the first course of chemotherapy, there was no significant difference in ECG and abnormal IMA incidence rates between the TC groups and EC groups (P > 0.05). After the third course and at the end of the sixth course, ECG and abnormal IMA incidence rates in the EC group were significantly higher than in the TC group (P < 0.05). Besides, IMA values significantly increased with the increase in chemotherapy courses in the EC group; and the value of the post-sixth course was significantly higher than in the pre- and post-first and -third courses of chemotherapy. IMA value in the post-sixth course in the TC group was significantly higher than that in the pre- and post-first and -third courses of chemotherapy. In addition, IMA values at the post-first and -third courses of chemotherapy in the EC group were significantly higher than in the TC group. Both EC and TC chemotherapy regimens were harmful to the myocardium, and the incidence rate of myocardial damage increased with the increase of cumulative dose. Besides, the degree of myocardial damage in EC group was significantly higher than in the TC group.

Abbreviations: CTX = cytoxan, EC = epirubicin combined with cyclophosphamide, ECG = electrocardiograph, EPI = epirubicin, HSA = human serum albumin, IMA = ischemia-modified albumin, TC = docetaxel combined with cyclophosphamide.

Keywords: anthracycline, docetaxel, ischemia-modified albumin, myocardial damage

1. Introduction
At present, the anthracycline represented by epirubicin (EPI) and the taxanes represented by docetaxel are the bases of breast cancer chemotherapy regimens, which are characterized with strong antitumor activity.[11] However, potential myocardial injuries induced by these 2 types of drugs not only affect the prognosis of patients, but also limit their applications in clinic.[2,3] Myocardial damages caused by chemotherapy drugs are divided into acute, subacute, tachycardias or bradycardias, pericardial effusion, and heart failure. Once it developed into congestive heart failure, mortality can reach as high as 48%. [14,5] Therefore, it is of great significance to timely screening and early drug intervention for patients with reversible myocardial injury. Current diagnostic methods of myocardial damage used in clinic include electrocardiograph (ECG), Doppler echocardiography, brain natriuretic peptide, cardiac troponin-T, and creatine kinase-MB fraction levels.[6,7] Among these, ECG has the best cost performance and is most commonly used. For patients with acute or subacute myocardial damage which usually caused by edema of myocardial cells and myocardial cell vacuolar degeneration, the ECG manifested with nonspecific ST-T (ST segment-T wave) alternations, lowing and flattening of QRS wave (QRS complex), and prolongation of QT interval. However, for patients with chronic myocardial damage, the changes in ECG signs are transient and not easy to be captured.[8–10] A simple ECG detection cannot instantly reflect the degree of myocardial damage in patients after chemotherapy, and commonly used clinical cardiac markers are lack of enough sensitivity and specificity for detection.[6,8]

Ischemia-modified albumin (IMA) is produced by human serum albumin (HSA) which local structure changed when it flows through ischemic tissues. Local tissues can produce oxidative stress reaction when myocardial ischemia occurred, and the N-terminal amino acid sequence of albumin was oxidatively modified, which result in IMA formation. IMA concentration rapidly increased in 5 to 10 minutes postmyocardial ischemia in peripheral blood, and sustained increase during the course of ischemia, it would lasted for 2 to 4 hours, and returned to baseline level in 6 to 10 hours.[11,12] Since it can be detected in the reversible phase of myocardial injury, and possesses the advantages of high sensitivity, high negative predictive value and early appearing,[13] it has become a hot topic in clinical research.
Therefore, we attempted to determine the relationship between the IMA—changes and ECG alternations—caused by EPI and docetaxel, and to assess the value of IMA combined with ECG as the diagnosis of the degree of drug-induced myocardial damage.

2. Materials and methods

2.1. General data

Patients who diagnosed with breast cancer by pathology and received postoperative adjuvant chemotherapy from the Breast Surgery Department of Qingdao Center Hospital and treated from January 1, 2014 to January 1, 2015 were enrolled into this study. All patients were female, and the age of these patients ranged from 24 to 59 years old. All patients were initially diagnosed with breast cancer and pathologically confirmed as invasive ductal carcinoma. Besides, in these patients, tumor node metastasis staging was I to II, physical status scored ≤2 points, expected survival period was 1 year, and routine blood and liver kidney function tests were normal. In addition, other malignant tumors were excluded, there were no previous and kidney function tests were normal. In addition, other serious heart diseases, there were no previous malignant tumors were excluded, there were no previous histories of coronary heart disease, angina, myocardial infarction, heart failure, and other serious heart diseases, there were no previous histories of radiotherapy and chemotherapy, no postoperative radiotherapy were performed in patients during the gestation and suckling period. According to the principle of informed consent, and approved by the local ethics committee, a total of 101 patients were randomly divided into 2 groups: EPI combined with cyclophosphamide (EC) group (n=55) and docetaxel combined with cyclophosphamide (TC) group (n=56).

There were no statistical differences in age distribution, tumor size, lymph node metastasis, and other general information between the 2 groups (P > 0.05) (Table 1).

2.2. Treatment method

Regimen in the EC group: An intravenous drip of 100mg/m² of EPI (Pfizer Pharmaceutical Wuxi Co., Ltd., Wuxi City, Zhejiang Province China, Pfizer, batch number: H20000496) was administered at the first day; an intravenous drip of 600mg/m² of cytoxan (CTX, manufactured by Jiangsu Hengrui Medicine Co., Ltd., Lianyungang City, Jiangsu Province China, batch number: 131012) was administered at the first day, every 21 days as an course, and sustained treatment for 6 courses. Regimen in the TC group: An intravenous drip of 75mg/m² of docetaxel (Taxotere; Aventis Pharma, Hangzhou City, Zhejiang Province China, batch number: H20030540) was administered at the first day; an intravenous drip of 600mg/m² of CTX (manufactured by Jiangsu Hengrui Medicine Co., Ltd., batch number: 131012) was administered at the first day, every 21 days as an course, and sustained treatment for 6 courses.

2.3. Observation

ECG examinations were performed on these 2 groups of patients before and at the end of the first, third, and sixth courses of chemotherapy. Besides, the conditions of nodal tachycardia, ventricular arrhythmia, atrial fibrillation, atrial tachycardia ST-T changes, and limb lead QRS low voltage were observed. IMA test: combination of albumin and cobalt ions is used to measure and Roche COBAS8000 is used to detect and reagent whose manual shows that IMA < 85kU/L is normal reference value. A unit of 2mL of peripheral venous blood was collected at pre- and postchemotherapy, anticoagulated with heparin, and IMA level was detected by enzyme-linked immunosorbent assay. If IMA value was ≥85kU/L, the result was considered as positive.

2.4. Statistical methods

SPSS 18.0 software (SPSS Inc, Chicago, IL) was used for statistical analysis, count data were expressed with the number of cases (constituent ratio), and χ²-test was used for comparison between groups. P < 0.05 was considered statistically significant. Measurement data were expressed as mean ± standard deviation (x ± s), and t test was used for comparisons between groups, analysis of variance was used in above 3 groups. P < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of the abnormal occurrence rates of ECG and IMA at the end of the different courses

No difference in abnormal occurrence rates of ECG and IMA were found in patients who received EC and TC chemotherapy at the end of the first course of chemotherapy (χ² = 2.03, χ² = 1.01; P > 0.05). Besides, at the end of the third course, the abnormal occurrence rates of ECG and IMA in the EC group were higher than in the TC group (χ² = 3.95, χ² = 2.04; P < 0.05); and at the end of the sixth course, the abnormal occurrence rates of ECG and IMA in the EC group were significantly higher than in the TC group (χ² = 7.15, χ² = 7.15; P < 0.05) (Table 2 and Fig. 1).

### Table 1

| Number | EC | TC | χ² | P   |
|-------|----|----|----|-----|
| Age, y | 50.2 ± 10.2 | 51.5 ± 9.7 | 0.476 | > 0.05 |
| Tumor size, cm | 2.5 ± 0.6 | 2.3 ± 0.5 | 1.91 | > 0.05 |
| Lymph node metastasis (+) (n), % | 32 (57.1) | 29 (52.7) | 0.219 | > 0.05 |
| ER (+) (n), % | 39 (69.6) | 36 (65.4) | 0.222 | > 0.05 |
| HER-2 (+) (n), % | 23 (41.0) | 19 (34.5) | 0.502 | > 0.05 |

EC = epirubicin combined with cyclophosphamide. ER = estrogen receptor. HER-2 = human epidermal growth factor receptor-2. TC = docetaxel combined with cyclophosphamide.

### Table 2

| Groups periods | Epirubicin | Docetaxel | P   | χ²  | Epirubicin | Docetaxel | P   | χ²  |
|---------------|-----------|-----------|-----|-----|-----------|-----------|-----|-----|
| At the end of the first course | 1 | 0 | > 0.05 | 1.01 | 2 | 0 | > 0.05 | 2.03 |
| At the end of the third course | 4 | 2 | < 0.05 | 2.036* | 8 | 2 | < 0.05 | 3.95* |
| At the end of the sixth course | 13 | 5 | < 0.05 | 7.15* | 13 | 5 | < 0.05 | 7.15* |

Compared with docetaxel. ECG = electrocardiograph. IMA = ischemia-modified albumin.

* P < 0.05.
3.2. Changes of IMA (kU/L) at the end of the different courses in the EC group and TC group

There was no difference in IMA values between the EC and TC groups before chemotherapy. In the EC group, IMA value significantly increased at the end of the third and sixth courses of chemotherapy, as compared with before chemotherapy (q = 5.584, P < .05; q = 11.90, P < .05; respectively); and this value significantly increased at the end of the third and sixth courses of chemotherapy, compared with the end of the first course of chemotherapy (q = 4.96, P < .05; q = 11.28, P < .03; respectively). In addition, this value significantly increased at the end of the sixth course, compared with the end of the third course of chemotherapy (q = 6.31, P < .05). In the TC group, IMA value at the end of the sixth course of chemotherapy significantly increased, compared with before and at the end of the first and third courses of chemotherapy (q = 6.62, 6.41, and 5.68, respectively; P < .05). There were no differences between the postthird course of chemotherapy versus the pre- and postfirst course of chemotherapy (q = 0.93, 0.73; P > .05). Besides, there was no significant difference in IMA values between the EC and TC group at the first course of chemotherapy (t = 0.077, P > .05). However, this difference was significant at the third course (t = 3.214, P < .05). At the end of the sixth course, the difference was statistically significant (t = 3.23, P < .05) (Table 3 and Fig. 2).

4. Discussion

Chemotherapy regimens containing anthracycline and docetaxel have been widely used in patients with breast cancer. These 2 kinds of chemotherapeutic drugs are characterized with a wide antitumor spectrum and strong anticancer activity. However, their toxic effects on heart are significant; various arrhythmias could be found in the early stage of damage, and heart failure would occur if the damage is severe.

The mechanism research of myocardial injury induced by anthracycline is mainly focused on the aspects of free radical, mitochondrial damage, and calcium overloading. Most researchers have accepted the theory of free radicals, in which the formation of free radicals could be induced. However, free radicals have anticancer activity and can also cause oxidative stress in heart and aggravate the damage of myocardial tissue.[8,14]

Taxanes are natural products isolated from taxus plants. They can terminate mitosis and trigger apoptosis of tumor cells by inhibiting microtubule depolymerization. These drugs can also cause cardiac toxicity with manifestations of ECG alternations,
which may be related to the oxidative stress of free radicals in myocardial cells.\(^{[9,10,15,16]}\)

As a marker of myocardial injury, IMA is a substance produced by HSA, local structure of which changed when it flew through the ischemic tissue. Albumin is the most abundant protein in human plasma. When the myocardium was locally oxidatively stressed, local hydroxyl radical increased. Albumin was damaged by the hydroxyl radical, which resulted in the formation of IMA. Roy et al.\(^{[17]}\) pointed out for the first time that the formation of IMA is directly related to the formation of active oxidation products and confirmed that hydroxyl radicals play an important role in the formation of IMA. Once these free radicals in local myocardium increased, an increase in IMA would be subsequently induced.\(^{[13,18–22]}\)

Nowadays, IMA is often used in testing ischemic disease, and especially for acute myocardial ischemia, has high sensitivity. In 2003, Food and Drug Administration of the United States of America approve IMA as biochemical marker of early myocardial ischemia. Through analysis of IMA for the emergency patients with suspected chest pain, Peacock et al.\(^{[23]}\) found that sensitivity to IMA is 80% and positive predictive value is 91%. Oxygen free-radical increases in the ischemic disease. So far, IMA has been applied to diagnose stroke, lower limb ischemia, and pulmonary embolism in the early state.\(^{[24–26]}\)

These above theories indicate that myocardial damage would occur in the applications of anthracycline and docetaxel drugs; and when damage occurs, it would cause IMA changes. Therefore, the sensitivity of IMA is very high. Combined with the changes in ECG, IMA can be used as an indicator to determine early myocardial damage induced by these 2 kinds of chemotherapeutic agents. From these experimental results, we could find that the incidence rate of myocardial damage induced by taxanes was lower than that induced by anthracycline; Abnormities in ECG and the positive rates of IMA in different courses of chemotherapy in the TC group were significantly lower than those in the EC group (\(P > 0.05\)), and myocardial damage occurred in a dose-dependent manner, as dosage increased, the occurrence of myocardial damage also increased. So was the circumstance in the EC group, the occurrence of myocardial damage increased as the dosage increased.

Our research does have limitations. On the one hand, the limitation is that chemotherapy here specifically talking about anthracycline and docetaxel chemotherapy, rather than a more general chemotherapy. On the other hand, there is the lack of follow-up studies data about the degree of myocardial ischemia recover between anthracycline and docetaxel chemotherapy. Therefore, the credibility could be affected. We have since established a standard to ensure that future studies do not encounter this difficulty.

**References**

[1] Di Marco A, Gaetani M, Scarpinato B, Adriamycin (NSC-123,127): a new antibiotic with antitumor activity. Cancer Chemother Rep 1969; 53:33–7.

[2] Mistaen WP. Cancer in heart disease patients: what are the limitations in the treatment strategy? Future Cardiol 2013;9:535–47.

[3] Chargari C, Kirov KM, Boller MA, et al. Cardiac toxicity in breast cancer patients. From a fractional point of view to a global assessment. Cancer Treat Rev 2011;37:521–30.

[4] Studooly PW, Richards DA, Meekle SR, et al. The potential role of echocardiographic strain imaging for evaluating cardiotoxicity due to cancer therapy. Heart Lung Circ 2011;20:3–9.

[5] Ellis P, Barrett-Lee P, Johnson L, et al. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. Lancet 2009;373:1681–92.

[6] Polumbo I, Palumbo B, Fravolini ML, et al. Brain natriuretic peptide as a cardiac marker of transient radiotherapy-related damage in left-sided breast cancer patients: a prospective study. Breast 2016;25:45–50.

[7] Steuter J, Bociek R, Loberiza F, et al. Utility of prechemotherapy evaluation of left ventricular function for patients with lymphoma. Clin Lymphoma Myeloma Leuk 2015;15:29–34.

[8] Ma Y, Kang W, Yao Y, et al. Clinical significance of ischemia-modified albumin in the diagnosis of doxorubicin-induced myocardial injury in breast cancer patients. PLoS One 2013;8:e79426.

[9] Jekunen A, Heikkinen P, Masche A, et al. Paclitaxel-induced myocardial damage detected by electron microscopy. Lancet 1994;343:727–8.

[10] Cao H, Yang W, Wang Q, et al. Taxol prevents myocardial ischemia-reperfusion injury by inducing JNK-mediated HO-1 expression. Pharm Biol 2016;54:551–60.

[11] Dominguez-Rodriguez A, Abreu-Gonzalez P. Current role of ischemia-modified albumin in routine clinical practice. Biomarkers 2010;15: 653–62.

[12] Kocak C, Kocak FE, Akcilar R, et al. Molecular and biochemical evidence on the protective effects of embelin and carnosic acid in isoproterenol-induced acute myocardial injury in rats. Life Sci 2016; 147:15–23.

[13] Mehta MD, Marwah SA, Ghosh S, et al. A synergistic role of ischemia-modified albumin and high-sensitivity troponin T in the early diagnosis of acute coronary syndrome. J Family Med Prim Care 2013;2:470–5.

[14] Zhang YW, Shi J, Li YJ, et al. Cardiomyocyte death in doxorubicin-induced cardiotoxicity. Arch Immunol Ther Exp (Warsz) 2009;57: 435–45.

[15] Hanna AD, Janczura M, Cho E, et al. Multiple actions of the anthracycline daunorubicin on cardiac ryanodine receptors. Mol Pharmacol 2011;80:538–49.

[16] Liv I, Mattru I, Scotti V, et al. Pegylated liposomal doxorubicin and oral vinorelbine in first line metastatic breast cancer patients previously treated with anthracyclines. J Chemother 2011;23: 158–62.

[17] Roy D, Quiles J, Gaze DC, et al. Role of reactive oxygen species on the formation of the novel diagnostic marker ischaemia modified albumin. Heart 2006;92:1134–6.

[18] Talwalkar SS, Bon Homme M, Miller JJ, Elin RJ. Ischemia modified albumin, a marker of acute ischemic events: a pilot study. Ann Clin Lab Sci 2008 Spring;38:132–7.

[19] Sharouni E, Georgiadou P, Voudris V. Ischemia modified albumin changes-review and clinical implications. Clin Chem Lab Med 2011; 49:177–84.

[20] Ocztasy Y, Trechter CG, Gabrielson KL, et al. DOX-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. Mol Cell Cardiol 2012;52:1213–25.

[21] Shalenkova MA, Mukhametova ET, Mikhailova ZD. The role of necrosis and inflammation markers in prognostication of acute coronary heart disease. Klin Med (Mosk) 2013;91:14–20.

[22] Dalamaga M, Kasazin K, Triantafylidh I, et al. Kinetics of serum ischemia-modified albumin during cardiopulmonary exercise testing in relation to metabolic and cardiac markers: a pilot study. Metabolism 2014;63:65–6.

[23] Peacock F, Morris DL, Anwaruddin S, et al. Meta-analysis of ischemic-modified albumin to rule out acute coronary syndrome in the emergency department. Am Heart J 2006;152:253–62.

[24] Peacock FJ, Morris DL, Anwaruddin S, et al. Ischemia-modified albumin in acute stroke. Cerebrovasc Dis 2007;23:216–20.

[25] Tureid S, Gumbuz A, Memese A, et al. The value of ischemia-modified albumin compared with D-dimer in the diagnosis of pulmonary embolism. Respir Res 2008;9:49.

[26] Roy D, Quiles J, Sharma R, et al. Ischemia-modified albumin concentrations in patients with peripheral vascular disease and exercise-induced skeletal muscle ischemia. Clin Chem 2004;50: 1656–60.