Anthracycline-Induced Microcirculation disorders: AIM PILOT Study

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INTRODUCTION

Anthracyclines are the basic therapy for a wide range of solid tumors and hematologic cancers. Anthracyclines remain an important therapeutic option in breast cancer. However, their use is limited by the risk of therapy-related cardiovascular toxicity (CTR-CVT) [1–3]. One of the symptoms of cardiovascular complications from anthracycline use is left ventricular systolic dysfunction. A less known side effect of anti-cancer medications is coronary microcirculation damage [4]. Single reports from experimental studies indicate simultaneous irreversible coronary microcirculation dysfunction (CMD) following exposure to anthracyclines [1]. Many processes leading to the apoptosis of cardiomyocytes undoubtedly involve also vascular endothelial cells, causing their damage and CMD at the same time. Invasive assessment of microcirculation using the index of microcirculatory resistance (IMR) measurement is currently the gold standard in the diagnosis of CMD [4]. It has already been tested on many groups of patients, including stable angina pectoris, acute STEMI, and post-heart transplantation [5]. The advantage of IMR over coronary flow reserve (CFR) is that the IMR measurement is simple, microvascular-specific, quantitative, reproducible, and independent of hemodynamic changes. CMD-associated ischemia increases the risk of major adverse cardiovascular events (MACE) [6, 7]. In selected groups of patients, e.g. after heart transplantation, with hypertrophic cardiomyopathy or ST-segment elevation myocardial infarction, the severity of CMD is a significant independent risk factor for clinical deterioration and death [5, 8, 9].

This study aimed to assess the coronary microcirculation dysfunction in patients with ischemia with non-obstructed coronary artery disease (INOCA) treated with anthracyclines for malignancy.

METHOD

The study presents a retrospective analysis of five consecutive patients previously treated oncologically with typical angina pectoris symptoms, in whom coronary arteriography revealed no significant coronary artery stenosis (stenosis <40% of vessel diameter or 40%–60% of vessel diameter assessed as insignificant in functional testing such as fractional flow reserve [FFR> 0.80], Table 1). All patients were evaluated for CMD using the Coroventis CoroFlow Cardiovascular System (Abbott Vascular, Santa Clara, CA, US). CFR and IMR were assessed as part of the diagnosis of INOCA. CMD was diagnosed when IMR ≥25 and/or CFR <2.0.

Moreover, 12-lead ECG, transthoracic echocardiography, and laboratory tests, including myocardial dysfunction marker assays, were performed in all patients. Table 1 shows the clinical characteristics of patients along with detailed data on the chemotherapy used. Patients were assessed based on the following exclusion criteria: previous radiotherapy, the presence of an acute inflammatory condition (hs-CRP>10 mg/l), systemic connective tissue diseases, treatment with interferon, bleeding diathesis due to platelet or plasma disorders, acute renal failure or chronic kidney disease with GFR <30 ml/min/1.73 m^2, allergy to iodinated contrast media, regadenoson, adenosine, uncontrolled asthma,

Table 1. Clinical characteristics of patients and the results of the microcirculation assessment

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, years	57	59	61	59	54
Sex	Female	Female	Female	Female	Female
BMI, kg/m^2	26	26	27	28	35.9
NYHA class	II	II	II	III	II
CCS class	III	III	III	III	III
HA	Yes	no	Yes	No	Yes
DM	Yes	no	Yes	No	No
Nicotinism	No	yes	No	No	No
Echocardiography					
EF, %	55	25	35	43	60
GLS, %	–14	–10	–11	–8	–18
EDD, mm	48	69	54	56	47
LAVI, ml/m^2	34	66	39	62	24
Location of the cancer	Breast	Ovarian	Lymphoma	Breast	Breast
Time since the end of chemotherapy, months	13	11	13	6	15
Type of chemotherapy					
Doxorubicin	Yes	No	Yes	Yes	Yes
Dosage, mg/m^2	240	0	420	240	240
Cyclophosphamide	Yes	No	Yes	Yes	Yes
Cisplatin	No	Yes	No	No	No
Docetaxel	Yes	No	No	Yes	Yes
Trastuzumab	No	No	No	Yes	Yes
Chest radiotherapy	No	No	No	No	No
Laboratory tests					
NT-proBNP, pg/ml	450	11595	5300	1639	2060
Troponin, ng/ml	0	0.03	0.03	0.7	0.012
LDL-C, mmol/l	1.8	2.6	1.6	5.7	3.2
eGFR, ml/min/1.73 m^3	78	26	61	56	90
Hb, mmol/dl	7.2	6.6	6.4	7.1	7.5
Drugs used					
Beta-blocker	Yes	Yes	Yes	Yes	No
ACEI/ ARB	Yes	No	Yes	Yes	Yes
Ca-blocker	No	No	No	No	Yes
ARNI	No	Yes	No	No	No
SGLT-2	No	Yes	Yes	No	Yes
Statin	No	Yes	Yes	Yes	No
Antidiabetic drugs	No	No	Yes	No	No
Insulin	No	No	Yes	No	No
Assessment of the coronary microcirculation:					
CFR	1.9	3.2	2.4	1.9	1.6
IMR	32	10	39	37	62
FFR	0.91	0.9	0.86	0.94	0.93

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARNI, angiotensin receptor-nephrilysin inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; NT-proBNP, N-terminal pro hormone B-type natriuretic peptide; CCS, Canadian Cardiovascular Society; CFR, coronary flow reserve; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EDD, end-diastolic diameter; EF, ejection fraction; ESD, end-systolic diameter; FFR, fractional flow reserve; GLS, global longitudinal stress; HA, hypertension; Hb, hemoglobin; IMR, index of microvascular resistance; LAVI, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; NYHA, New York Heart Association

2nd and 3rd-degree atrioventricular block, or lack of informed consent.

RESULTS AND DISCUSSION

All five described patients had cancer. Three of them were diagnosed with breast cancer, one with lymphoma, and one with ovarian cancer. Four patients received chemotherapy with anthracyclines, while the ovarian cancer patient was administered cisplatin-based chemotherapy. On admission, all patients had symptoms of typical class III angina pectoris as defined by the Canadian Cardiovascular Society. None of the patients under analysis had been previously diagnosed with cardiovascular diseases. Left ventricular ejection fraction (LVEF) varied between 25% and 60%. The highest dose of anthracyclines was administered to the patient treated for lymphoma.

All patients underwent invasive coronary angiography, and then, due to no significant lesions in coronary arteries, a simultaneous assessment of coronary microcirculation was performed. CMD with a significantly increased IMR was revealed in all patients who were administered anthracyclines in the past. The patient who received non-anthracyclines chemotherapy presented normal coronary microcirculation function despite significantly impaired ejection fraction.

The presence of anthracyclines-related cardiotoxicity was proportional to the dose administered — the higher the dose, the higher the probability. With a dose of 400 mg/m^2, the risk of symptomatic heart failure (HF) was 3%, with 550 mg/m^2 — 7% and with doses of 700 mg/m^2 — as many as 18% [2]. The risk of cardiotoxicity increased up to 35% if defined as an abnormal increase in cardiac biomarkers, such as troponin or NT-proBNP. It should be noted that no cardiac-safe dose of anthracyclines was determined. Persons with higher risk of cardiotoxicity include patients over 65 years, women, persons with low body weight, persons with a history of heart disease as well as patients who underwent chest radiotherapy [10].

The damage to coronary microcirculation due to anthracyclines administration is a new issue. In animal models, upon anthracyclines administration, permanent microcirculation damage was detected already at the subclinical stage [11]. Both a decrease in the density of the capillary network and dysfunction of other microcirculation vessels were demonstrated. Several mechanisms of anthracycline cardiotoxicity were proposed. Oxidative stress, initiated by doxorubicin, causes mitochondrial damage, which then leads to the apoptosis of both cardiomyocytes and endothelial cells. Moreover, through inhibition of topoisomerase IIb, therapeutic doses of doxorubicin can lead to direct DNA damage to endothelial cells and their further apoptosis in the non-oxidative mechanism [12]. Sodium-calcium and sodium-potassium pumps (Na+/K+-*ATP*ase) also become damaged, which leads to the cells being overloaded with calcium ions and the death of the myocyte.

Our study has shown that CMD occurs both in patients with evident left ventricular systolic function damage and in patients with normal or slightly reduced ejection fraction. In line with the experimental studies, this may indicate that CMD clinically precedes evident cardiomyocyte dysfunction. Taking into account the irreversible cardiotoxicity mechanism of anthracyclines, by detecting this process at the stage of microcirculation and initiating cardio-protection, we can prevent patients from developing evident heart failure. The above hypothesis undoubtedly needs to be confirmed in subsequent prospective studies.

Article information

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REFERENCES

1. Grakova EV, Shilov SN, Kopeva KV, et al. Anthracycline-Induced Cardiotoxicity: The Role of Endothelial Dysfunction. Cardiology. 2021; 146(3): 315–323, doi: 10.1159/000512771, indexed in Pubmed: 33596565.
2. Agunbiade T, Zaghlol R, Barac A. Heart Failure in Relation to Anthracyclines and Other Chemotherapies. Methodist Debakey Cardiovasc. 2019; 15(4): 243–249, doi: 10.14797/mdcj-15-4-243, indexed in Pubmed: 31988684.
3. Lyon A, López-Fernández T, Couch L, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. Eur Heart J. 2022; 43(41): 4229–4361, doi: 10.1093/eurheartj/ehac244, indexed in Pubmed: 36017568.
4. Cuculi F, De Maria GL, Meier P, et al. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2014; 64(18): 1894–1904, doi: 10.1016/j.jacc.2014.07.987, indexed in Pubmed: 25444143.
5. Clarke JRD, Kennedy R, Duarte Lau F, et al. Invasive Evaluation of the Microvasculature in Acute Myocardial Infarction: Coronary Flow Reserve versus the Index of Microcirculatory Resistance. J Clin Med. 2019; 9(1), doi: 10.3390/jcm9010086, indexed in Pubmed: 31905738.
6. Taqueti VR, Everett BM, Murthy VL, et al. Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. Circulation. 2015; 131(6): 528–535, doi: 10.1161/CIRCULATIONAHA.114.009716, indexed in Pubmed: 25480813.
7. Taqueti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. Circulation. 2015; 131(1): 19–27, doi: 10.1161/CIRCULATIONAHA.114.011939, indexed in Pubmed: 25400060.
8. Majmudar MD, Murthy VL, Shah RV, et al. Quantification of coronary flow reserve in patients with ischaemic and non-ischaemic cardiomyopathy and its association with clinical outcomes. Eur Heart J Cardiovasc Imaging. 2015; 16(8): 900–909, doi: 10.1093/ehjci/jev012, indexed in Pubmed: 25719181.
9. Neglia D, Michelassi C, Trivieri MG, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. Circulation. 2002; 105(2): 186–193, doi: 10.1161/hc0202.102119, indexed in Pubmed: 11790699.
10. Klotzka A, Kufel-Grabowska J, Zembala M, et al. Is anthracycline-induced heart failure reversible? Kardiol Pol. 2020; 78(12): 1295–1296, doi: 10.33963/KP.15637, indexed in Pubmed: 33021353.
11. Galán-Arriola C, Vílchez-Tschischke JP, Lobo M, et al. Coronary microcirculation damage in anthracycline cardiotoxicity. Cardiovasc Res. 2022; 118(2): 531–541, doi: 10.1093/cvr/cvab053, indexed in Pubmed: 33605403.
12. Cassina V, Seruggia D, Beretta GL, et al. Atomic force microscopy study of DNA conformation in the presence of drugs. Eur Biophys J. 2011; 40(1): 59–68, doi: 10.1007/s00249-010-0627-6, indexed in Pubmed: 20882274.