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Heart failure in chemotherapy-related cardiomyopathy: Can exercise make a difference?

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ABSTRACT

Medical therapies in oncology have resulted in better survival resulting in a large population who are at risk of early and late cardiac complications of chemotherapy. Cardiotoxicity related to chemotherapy can manifest decades after treatment with a threefold higher mortality rate as compared to idiopathic dilated cardiomyopathy. The leading cause of death in cancer survivors seems to be cardiac. Early detection and intervention could prevent progression of heart failure to end stage disease requiring advanced therapies such as implantation of ventricular assist devices or cardiac transplantation. This review focuses on the role of exercise in cardioprotection in this population. The current practice of depending on ejection fraction for diagnosis of heart failure is suboptimal to detect subclinical disease. It is also important to diagnose and treat early diastolic dysfunction as this tends to lead to heart failure with preserved ejection fraction. Hence we suggest an algorithm here that is based on using strain rate and tissue Doppler imaging modalities to detect subclinical systolic and diastolic dysfunction. Further research is warranted in terms of defining exercise prescriptions in this population. Human studies with multicenter participation in randomized controlled trials should be done to elucidate the intricacies of aerobic exercise intervention in cardiotoxicity dependent heart failure. It is also necessary to assess the utility of exercise interventions in the different chemotherapeutic regimens as they impact the outcomes.

Contents

1. Introduction

The impressive development of medical therapies in oncology has resulted in better survival and consequently in a large population of survivors who are at risk of early and late cardiac complications secondary to chemotherapy. Chemotherapy-related cardiomyopathy (CRC) can manifest decades after treatment with a threefold higher mortality rate as compared to idiopathic dilated cardiomyopathy [1]. The 5-year survival rate for all cancers in the US has increased from 50% in 1975–1977 to 68% in 1999–2005. The leading cause of death in cancer survivors seems to be cardiac [1–4]. This review focuses on the possible role of exercise in preventing onset and progression of heart failure in CRC patients and attempts to highlight the need for more detailed

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studies required to arrive at defined exercise prescriptions for patients treated with different chemotherapeutic agents.

1.1. Chemotherapy-related cardiotoxicity versus cardiac hypersensitivity

Cardiotoxicity can be defined as a direct effect of chemotherapy resulting in cardiac dysfunction which may lead to reversible/irreversible heart failure. From a retrospective review of trastuzumab clinical trials CRC has been defined as one or more of the following; a) reduction of LVEF (global or specific to the interventricular septum); b) symptoms or signs of heart failure (HF); c) decrease in LVEF from baseline ≤5% to <55% in the presence of signs or symptoms of HF, or a reduction in LVEF ≥10% to <55% without signs or symptoms of HF [5] Cardiotoxicity related cardiac dysfunction (CRCD) is divided into 2 types. Type I consists of cardiac disease secondary to anthracycline. Increased production of oxygen free radicals and oxidative stress with abnormalities in mitochondrial metabolism as well as lysosomal structure and function has been attributed to be the etiology of cardiotoxicity [6]. Anthracyclines are also noted to impair iron metabolism and therefore cause iron accumulation in the cardiac myocytes [7]. Many factors including cumulative dosage of anthracycline as well as concomitant use of other drugs, age and female gender have been implicated in the toxicity noted [8,9]. Type II is induced by trastuzumab. Trastuzumab is a monoclonal, humanized antibody. It is FDA approved for treatment of HER2 positive breast cancers. Cardiotoxicity secondary to trastuzumab has been noted to be reversible status post-discontinuation of the drug and well-tolerated on repeat dosing. Patients show reduced ejection fraction but are asymptomatic with no overt heart failure [10–12]. However when dosed with anthracyclines it is known to worsen the cardiotoxicity.

Cardiac hypersensitivity reactions should be distinguished from cardiotoxicity produced by chemotherapeutic agents. The cardiovascular system acts both as a source as well as a target for mediators of allergic reactions. Mast cells reside largely around the adventitia of large coronary arteries in close apposition with the small intramural vessels. Cardiac mast cells respond to IgE-mediated stimuli [13,14], and can also be activated by other stimuli such as anaphylatoxins (C3a and C5a), substance P and eosinophilic cationic proteins [14]. With increase in use of chemotherapeutic agents there is a concomitant increase in incidence of hypersensitivity reactions. Premedication, skin testing, and desensitization protocols may be useful in abating these reactions especially in patients with a history of hypersensitivity [15,16].

1.2. Role of cardiovascular imaging in defining cardiotoxicity

A number of chemotherapeutic agents have been linked to heart failure with reduced ejection fraction (HFrEF) with one of the topmost offenders being the anthracyclines [17]. Left ventricular ejection fraction (LVEF) is usually assessed at baseline and following every cycle but no definite universal guidelines exist for the frequency of these examinations in different chemotherapeutic regimens. In the 2012 guidelines by the European Society of Medical Oncology (ESMO) the frequency of echocardiographic surveillance has been discussed essentially for patients undergoing treatment with anthracycline regimens [18]. Different modalities ranging from 2D echocardiography to cardiac magnetic resonance are used in different institutions to assess left ventricular function making it highly non-uniform and variable. Stress echocardiography may detect cardiomyopathy at the subclinical level, so that early treatment could be initiated before heart failure progresses to an irreversible stage [19]. Strain rate imaging is a new modality using echocardiographic techniques to assess early subclinical disease [20–22].

Tissue Doppler imaging is the most widely used technique for assessing diastolic dysfunction currently. Cardiac troponin I (cTnI) and brain natriuretic peptide (BNP) are also used for risk stratification and prognostication [23–24]. Early identification of patients who are susceptible to cardiotoxicity may prevent morbidity and mortality [25–27].

Table 1 lists selected studies using different cardiovascular imaging techniques for predicting clinical outcomes in patients experiencing cancer therapy related cardiotoxicity [2,28–43]. Mutigated acquisition (MUGA), 2D and 3D echocardiography have been shown to be useful to varying degrees. Cardiac magnetic resonance (CMRI) still remains the gold standard. CMRI is limited due to the high cost of installation and operation as well as technical difficulties in patients with metallic prosthesis and devices. The pros and cons of each of the techniques are listed in Table 1. Noninvasive imaging continues to be used for assessing LVEF for risk stratification, diagnosis and prognosis. Many more investigations will be needed in the area of noninvasive imaging techniques for risk stratification and prognostication in this population.

Three-dimensional echocardiography-derived LVEF appears to be reliable in patients receiving chemotherapy [43]. Global longitudinal strain (GLS) and strain rate detect subclinical changes during chemotherapy, radiation and trastuzumab treatment before changes in LVEF are detectable [44]. In an athletic healthy population, cardiac strain changes are noted in response to exercise training [45]. GLS has been used in the oncology population to predict early subclinical changes [21]. GLS has been shown to be predictive of all-cause mortality in the heart failure population [46–49] but this remains to be demonstrated in cancer survivors.

Endothelial function and cardiac biomarkers can be used to predict and identify cardiotoxicity [50–52]. However both endothelial function and biomarkers need further testing and validation in the cancer population.

2. Clinical studies assessing benefits of exercise

Early detection and intervention may prevent progression of heart failure to Stage D requiring surgical therapies such as placement of a ventricular assist device or cardiac transplantation. However high level evidence is still lacking in clinical decision making regarding early detection and management of chemotherapy related cardiotoxicity [43]. Identification of subclinical disease prior to appearance of symptoms would be the key factor to prevent cardiovascular injury and enhance survival as well as quality of life. Additionally such a strategy would also help in initiating standard heart failure therapies ahead of time before the patient becomes symptomatic.

Studies including randomized clinical trials appear to be conducted in small groups of patients undergoing treatment for cancer notably of the breast. The highlights of these exercise studies point to increased VO2 max, decreased heart rate and decreases in systolic and diastolic blood pressure [53–58]. Interestingly, exercise therapy does not seem to prevent ventricular remodeling secondary to trastuzumab when used as adjuvant therapy [59] suggesting that combinations of chemotherapeutic agents may affect multiple molecular targets all of which may not be modulated by exercise. In a study of 123 women assigned to supervised, self-directed or standard care the best benefit in patients who underwent chemotherapy was in the self-directed exercise group. Supervised exercise was of benefit only in cancer patients not receiving any chemotherapy. No significant differences were noted between the groups in their quality of life assessment [60]. In a home-based walking study in stages 1–3 breast cancer patients who were starting first line adjuvant therapy significant benefits were observed. The exercise regimen was home-based and consisted of aerobic exercise and walking for 30 min 3 times a week. The patients appeared to benefit in terms of significant increase in VO2 max as well as 6 min walk test [61]. The studies on patients in the post-treatment period also seem to benefit from supervised as well as home based exercise regimen [62–65]. In a study of 113 women role of exercise during and after treatment was assessed. It was interesting that the group that had maximal benefit consisted of the women who underwent a prescriptive exercise program. These individuals showed improvement in the cardiopulmonary parameters as well as their fatigue levels suggesting that exercise intervention earlier could be beneficial [66]. Table 2 lists some of the recent

Table 1
Comparison of cardiovascular imaging techniques in defining cardiotoxicity.

Imaging	Parameter of cardiotoxicity	Pros	Cons	References
MUGA	LVEF	Reproducible calculation Low operator variability Serial testing is possible Comparable to CMR which is the gold standard	Gives no information on DD Involves radiation use Cannot detect subclinical disease	[28]
2DE	LVEF	Assesses systolic and diastolic function Tissue Doppler techniques assess diastolic function Non-invasive No radiation involved Serial testing is possible	High operator variability Preload dependence Cannot detect subclinical disease	[29,30]
RT3DE	LVEF	Assesses systolic and diastolic function Low operator variability Serial testing is possible More powerful than 2DE Comparable to CMR which is the gold standard	Preload dependence Cannot detect subclinical disease	[29,30,43]
SRI	GLS, LS	Detects subclinical disease and useful in prognostication Used in combination with 2DE	Vendor variability	[2,31–36,44]
CCT	Coronary calcium, LVEF, atherosclerosis	Assesses coronary atherosclerosis	No definite studies Contrast nephropathy	[37]
MRI	LVEF, high resolution of structure and function	Non-invasive No radiation involved Serial testing is possible Best correlation of structure and function Gold standard for LVEF determination Characterization of myocardial tissue	High cost Unavailable in all hospitals Requirement of advanced technology and skilled personnel Contraindicated with metal implants Gadolinium induced retroperitoneal fibrosis With renal insufficiency	[38–42]

randomized human studies defining the use of exercise regimens in heart failure secondary to cardiotoxicity.

3. Possible cellular and molecular basis of exercise induced changes in CRC

Anthracyclines in general cause severe cardiotoxicity via upregulation of the reactive oxygen species. It has been thought that this can happen as a two-pronged process because of the semi-quinone group generated via interactions with endothelial nitric oxide synthase inducing excessive free radical production [67]. Additionally it disrupts topoisomerase 2B activity which in turn can cause breaks in double-stranded DNA leading to activation of p53 tumor suppressor gene, increased reactive oxygen species (ROS) production, increased mitochondrial dysfunction and consequent cell dysfunction and death. ROS produced can independently increase protein, nucleic acid, lipid peroxidation increasing apoptosis and cell death. These effects are attenuated by aerobic exercise. Exercise causes upregulation of antioxidant and anti-apoptotic capacity.

At the molecular level the cardiac muscle is said to be protected by activation of pathways that use gp130 cytokines and neuregulin. Neuregulin-1 (NRG-1) is a paracrine factor produced by endothelial cells of the microvasculature and is upregulated in heart failure. Circulating levels of NRG-1β were assayed in heart failure patients and found to have significant prognostic value.

It was found to be independently associated with increased risk of mortality or need for cardiac transplantation and demonstrated significant correlations with NYHA class and disease severity. [68]. In another small study of chronic HF patients HER2 upregulated in chronic heart failure correlated significantly with New York Heart Association class [69]. The decreased NRG1/ErbB signaling and increases in angiotensin II and adrenergic agonists were combated by exercise by increasing mechanical stress and depression of the neurohormonal system. Additionally exercise appears to cause increases in myocardial AKT thereby decreasing pathological LV remodeling and hypertrophy [70–73].

When trastuzumab is dosed with anthracycline, it inhibits the ErbB2 receptor, resulting in loss of the neuregulin-dependent pathways and consequent death of cardiac myocytes. Another important

Table 2
Effect of exercise in chemotherapy patients.

Author	Study type	Type of chemotherapeutic agent	Subjects (n)	Type of exercise regimen	Conclusions
Corneya et al. [53,54]	Randomized Trial (RT)	Herceptin/taxane	242,301	Standard*, higher volume** and combination of resistance and aerobic exercise	Possible positive outcome in the higher volume group
Corneya et al. [54]	RT subgroup analysis	Herceptin/taxane	301	Standard*, higher volume** and combination of resistance and aerobic exercise	Women may benefit from the higher volume exercise regimen
Corneya et al. [55] (START)	RT	Adjuvant chemotherapy	242	Usual care, supervised aerobic and resistance training during chemotherapy	Exercise may improve outcomes (no statistical significance)
Corneya et al. [54,63]	RT	Herceptin/taxane	301,58		Higher volume exercise regimen or combined may be better than standard, better quality of life
Hornsby et al. [56]	RT	Doxorubicin/cyclophosphamide	20	Aerobic training	Aerobic training improved the VO2 max
Haykowsky et al. [59]	Observational	Trastuzumab adjuvant therapy	17	Aerobic exercise before and after treatment	No effect of aerobic exercise in left ventricular remodeling
Vincent et al. [61]	Observational	First line adjuvant therapy per protocol	39	Home based walking therapy	Significant improvement of VO2 max

* Standard dose = 25 to 30 minutes of aerobic exercise three times a week
** Higher volume = 50 to 60 minutes of aerobic exercise three times a week

aspect of trastuzumab toxicity stems from the fact that it downregulates AKT [74].

Exercise increases myocardial AKT and possibly counteracts the pathological effects. Cancer therapies that target vascular endothelial growth factor (VEGF) as well as the use of other molecularly targeted therapies such as tyrosine kinase inhibitors cause anti-angiogenesis which in turn affects cardiac function. Tyrosine kinase inhibitors affect a variety of enzymes resulting in mitochondrial dysfunction [75]. It has been hypothesized that exercise results in upregulation of VEGF and endothelial progenitor cells (EPCs) by activation of stat 3 which in turn causes erythropoietin mediated differentiation of cardiac progenitor cells into endothelial cells [73]. Fig. 1 shows a simplified view of the complex molecular mechanisms possibly underlying cardiotoxicity and the counteracting effects of exercise in this population.

4. Exercise prescription

Fig. 2 shows a suggested algorithm in cardiotoxicity induced by chemotherapeutic agents. The current practice of depending on ejection fraction for diagnosis of heart failure is suboptimal to detect subclinical disease. It is also important to diagnose and treat early diastolic dysfunction as this tends to lead to heart failure with preserved ejection fraction. This algorithm is based on utilizing strain rate and tissue Doppler imaging modalities to detect subclinical systolic and diastolic dysfunction and the use of exercise as tolerated.

5. Conclusions

Based on the existing literature it is imperative that further research is warranted in terms of defining exercise prescriptions in this population. Human studies with multicenter participation in randomized controlled trials should be done to elucidate the intricacies of aerobic exercise intervention in cardiotoxicity dependent heart failure. In the molecularly targeted therapies the use of aerobic exercise intervention is still debated. It is possible that the existing studies are small and not randomized and hence may not reflect the true benefit. This is an area that definitely calls for large randomized controlled trials to define exercise prescription. In addition, a better understanding of molecular mechanisms operating in aerobic exercise is needed. This will pave the way for larger studies which have adequate power to investigate the role of exercise in the patient populations in whom several different combinations of chemotherapeutic agents are used. Therefore a multidisciplinary approach involving other relevant specialties including exercise physiologists and physical medicine specialists would be beneficial in arriving at the right exercise prescriptions.

6. Future perspectives

Role of physical exercise for prevention of cardiovascular toxicity in the clinical setting still requires rigorous investigations. Most investigations have been done in breast cancer in the context of doxorubicin. Future investigations are warranted to assess exercise as a definite method for the reduction of cardiovascular morbidity and mortality in cancer survivors in general. Translation of preclinical experiments to the human system requires definition of sensitive diagnostic and outcome measures as well as an optimal exercise prescription.

The definition of an exercise prescription remains ambiguous. Though, moderate intensity exercise 3 times weekly was found to improve systolic function in heart failure patients [72], derivation of an optimal exercise prescription in the chemotherapy population needs further investigations as it is currently more challenging to balance exercise tolerance with defined improvements in protection of cardiac function. Existing studies use high intensity aerobic exercise regimens in animal models treated with chemotherapeutic agents as well as in the non-cancer heart failure populations [76,77] Such regimens may not be tolerated in patients undergoing cancer chemotherapy because of fatigue and deconditioning.

Use of exercise in the current literature is driven by improvements and functionality. Existing studies essentially focus on doxorubicin toxicity [78] hence it is imperative that future studies are needed to investigate toxicities of other drugs and combinations of chemotherapeutic agents. The dosage of these agents and duration of therapy also need to be investigated in the context of low, moderate and high intensity exercise regimens. Studies are lacking at this time also with respect to relevant improvements in cardiac function at the molecular and biochemical levels.

In animal model systems several studies exist to support exercise prevention [79–86]. Future clinical investigations in patients are needed to prescribe appropriate intensity, frequency, duration, and timing of exercise for primary and secondary prevention of cardiotoxicity resulting from the several different chemotherapeutic regimens that are currently available.

Disclosures

Drs. Nandini Nair and Enrique Gongora have no disclosures relevant to this work.

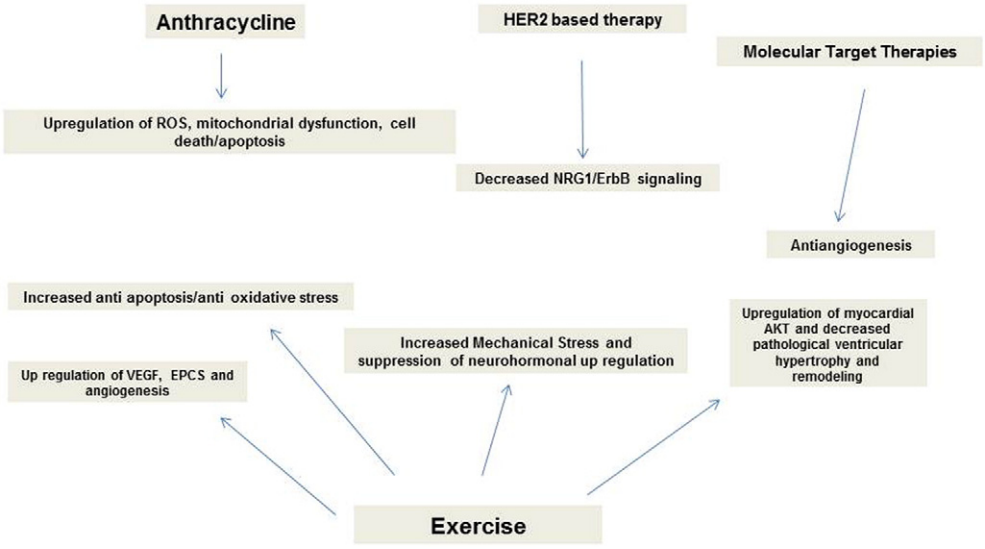

Fig. 1. Possible molecular mechanisms in exercise-induced changes in CRC.

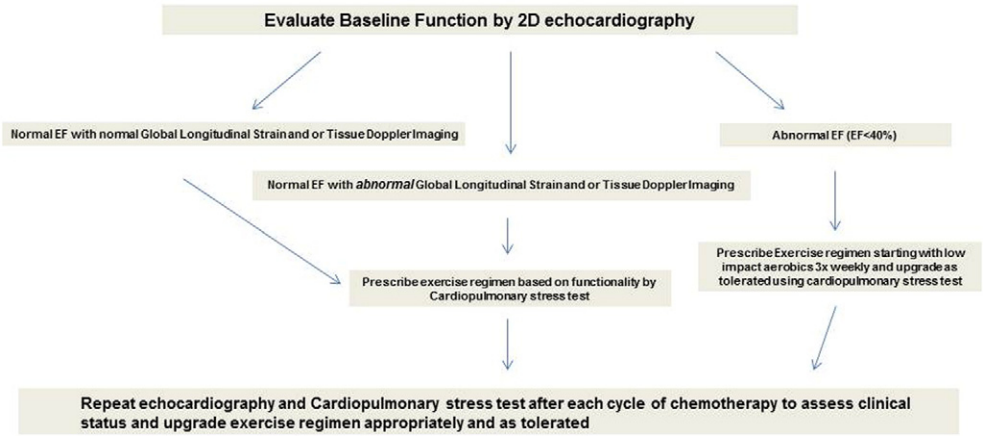

Fig. 2. Suggested exercise prescription in CRC.

Transparency document

The Transparency document associated with this article can be found, in online version.

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References

[1] M.T. Nolan, R.M. Lowenthal, A. Venn, T.H. Marwick, Chemotherapy-related cardiomyopathy: a neglected aspect of cancer survivorship, Intern. Med. J. 44 (2014) 939–950, http://dx.doi.org/10.1111/imj.12532.
[2] H.R. Villarraga, J. Herrmann, V.T. Nkomo, Cardio-oncology: role of echocardiography, Prog. Cardiovasc. Dis. 57 (2014) 10–18, http://dx.doi.org/10.1016/j.pcad.2014.05.002.
[3] R.G. Schwartz, D. Jain, E. Storozynsky, Traditional and novel methods to assess and prevent chemotherapy-related cardiac dysfunction noninvasively, J. Nucl. Cardiol. 20 (2013) 443–464, http://dx.doi.org/10.1007/s12350-013-9707-1.
[4] J. Herrmann, A. Lerman, N.P. Sandhu, H.R. Villarraga, S.L. Mulvagh, M. Kohli, Evaluation and management of patients with heart disease and cancer: cardio-oncology, Mayo Clin. Proc. 89 (2014) 1287–1306, http://dx.doi.org/10.1016/j.mayocp.2014.05.013.
[5] M. Florescu, M. Cinteza, D. Vinereanu, Chemotherapy-induced cardiotoxicity, Maedica (Buchar) 8 (2013) 59–67.
[6] P.K. Singal, C.M. Deally, L.E. Weinberg, Subcellular effects of adriamycin in the heart a concise review, J. Mol. Cell. Cardiol. 19 (1987) 817–828.
[7] J.C. Kwok, D.R. Richardson, Anthracyclines induce accumulation of iron in ferritin in myocardial and neoplastic cells inhibition of the ferritin iron mobilization pathway, Mol. Pharmacol. 63 (2003) 849–856.
[8] K. Shan, A.M. Lincoff, J.B. Young, Anthracycline-induced cardiotoxicity, Ann. Intern. Med. 125 (1996) 47–58.
[9] E. Yeh, C. Bickford, Cardiovascular complications of cancer therapy incidence pathogenesis diagnosis and management, J. Am. Coll. Cardiol. 53 (2009) 2231–2247, http://dx.doi.org/10.1016/j.jacc.2009.02.050.
[10] M. Ewer, S. Lippman, Type II chemotherapy-related cardiac dysfunction time to recognize a new entity, J. Clin. Oncol. 23 (2005) 2900–2902.
[11] T. Force, D.S. Krause, R.A. Van Etten, Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibitors, Nat. Rev. Cancer 7 (2007) 332–344.
[12] M.S. Ewer, M.T. Vooletich, J.B. Durand, M.L. Woods, J.R. Davis, V. Valero, D.J. Lenihan, Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment, J. Clin. Oncol. 23 (2005) 7820–7826.
[13] G. Marone, V. Patella, G. de Crescenzo, A. Genovese, M. Adt, Human heart mast cells in anaphylaxis and cardiovascular disease, Int. Arch. Allergy Immunol. 107 (1995) 72–75.
[14] V. Patella, I. Marino, B. Lamparter, E. Arbustini, M. Adt, G. Marone, Human heart mast cells. Isolation, purification, ultrastructure, and immunologic characterization, J. Immunol. 154 (1995) 2855–2856.
[15] S. Cortijo-Cascajares, M.J. Jiménez-Cerezo, A. Herreros de Tejada, Review of hypersensitivity reactions to antineoplastic agents, Farm. Hosp. 36 (2012) 148–158, http://dx.doi.org/10.1016/j.farma.2011.02.004.
[16] J. Boulanger, J.N. Boursiquot, G. Cournoyer, J. Lemieux, M.S. Masse, K. Almanric, M.P. Guay, Comité de l'évolution des pratiques en oncologie, Management of hypersensitivity to platinum- and taxane-based chemotherapy: review and clinical recommendations, Curr. Oncol. 21 (2014) e630–e641, http://dx.doi.org/10.3747/co.21.1966.
[17] A. Saidi, R. Alharethi, Management of chemotherapy induced cardiomyopathy, Curr. Cardiol. Rev. 7 (2011) 245–249.
[18] G. Curigliano, D. Cardinale, T. Suter, G. Plataniotis, E. de Azambuja, M.T. Sandri, C. Criscitiello, A. Goldhirsch, C. Cipolla, F. Roila, ESMO Guidelines Working Group, Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines, Ann. Oncol. 23 (Suppl. 7) (2012) vii155–vii166.
[19] E. Yeh, A. Tong, D. Lenihan, S.W. Yusuf, J. Swafford, C. Champion, J.B. Durand, H. Gibbs, A.A. Zafarmand, M.S. Ewer, Cardiovascular complications of cancer therapy diagnosis pathogenesis and management, Circulation 109 (2004) 3122–3131.
[20] B.C. Drafts, K.M. Twomley, R. D'Agostino, J. Lawrence, N. Avis, L.R. Ellis, V. Thohan, J. Jordan, S.A. Melin, F.M. Torti, W.C. Little, C.A. Hamilton, W.G. Hundley, Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease, JACC Cardiovasc. Imaging 6 (2013) 877–885, http://dx.doi.org/10.1016/j.jcmg.2012.11.017.
[21] N. Fallah-Rad, J.R. Walker, A. Wassef, M. Lytwyn, S. Bohonis, T. Fang, G. Tian, I.D. Kirkpatrick, P.K. Singal, M. Krahn, D. Grenier, D.S. Jassal, The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy, J. Am. Coll. Cardiol. 57 (2011) 2263–2270, http://dx.doi.org/10.1016/j.jacc.2010.11.063.
[22] K. Negishi, T. Negishi, B.A. Haluska, J.L. Hare, J.C. Plana, T.H. Marwick, Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection, Eur. Heart J. Cardiovasc. Imaging 15 (2014) 324–331, http://dx.doi.org/10.1093/ehjci/jet159.
[23] D. Cardinale, M.T. Sandri, A. Martinoni, E. Borghini, M. Civelli, G. Lamantia, S. Cinieri, G. Martinelli, C. Fiorentini, C.M. Cipolla, Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy, Ann. Oncol. 13 (2002) 710–715.
[24] T. Nousiainen, E. Vanninen, E. Jantunen, J. Puustinen, J. Remes, A. Rantala, O. Vuolteenaho, J. Hartikainen, Natriuretic peptides during the development of doxorubicin-induced left ventricular diastolic dysfunction, J. Intern. Med. 251 (2002) 228–234.
[25] E.C. van Dalen, H.N. Caron, H.O. Dickinson, et al., Cardioprotective interventions for cancer patients receiving anthracyclines, Cochrane Database Syst. Rev. (2008) CD003917, http://dx.doi.org/10.1002/14651858.CD003917.pub3.
[26] B.V. Jensen, T. Skovsgaard, S.L. Nielsen, Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients, Ann. Oncol. 13 (2002) 699–709.
[27] J.A. Tallaj, V. Franco, B.K. Rayburn, L. Pinderski, R.L. Benza, S. Pamboukian, B. Foley, R.C. Bourge, Response of doxorubicin-induced cardiomyopathy to the current management strategy of heart failure, J. Heart Lung Transplant. 24 (2005) 2196–2201.
[28] L.F. de Geus-Oei, A.M. Mavinkurve-Groothuis, L. Bellersen, M. Gotthardt, W.J. Oyen, L. Kapusta, H.W. van Laarhoven, Scintigraphic techniques for early detection of cancer treatment-induced cardiotoxicity, J. Nucl. Med. 52 (2011) 560–571, http://dx.doi.org/10.2967/jnumed.110.082784.
[29] R. Altena, P.J. Perik, D.J. van Veldhuisen, E.G. de Vries, J.A. Gietema, Cardiovascular toxicity caused by cancer treatment: strategies for early detection, Lancet Oncol. 10 (2009) 391–399, http://dx.doi.org/10.1016/S1470-2045(09)70042-70047.
[30] J. Walker, N. Bhullar, N. Fallah-Rad, M. Lytwyn, M. Golian, T. Fang, A.R. Summers, P.K., I. Barac, I.D. Kirkpatrick, D.S. Jassal, Role of three-dimensional echocardiography in breast cancer: comparison with two-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging, J. Clin. Oncol. 28 (2010) 3429–3436, http://dx.doi.org/10.1200/JCO.2009.26.7294.
[31] Y. Xu, J. Hermann, P.A. Pellikka, S.M. Ansell, S. Cha, H.R. Villarraga, Can early changes in 2-dimensional speckle tracking echocardiography predict a future decrease in left

ventricular ejection fraction in lymphoma patients undergoing anthracycline chemotherapy? J. Am. Soc. Echocardiogr. 26 (2013) B52.
[32] N. Sandhu, J. Spoon, J. Herrmann, P.A. Pellikka, H. Villarraga, Two dimensional speckle tracking echocardiography predicts preclinical cardiotoxicity in breast cancer patients, J. Am. Coll. Cardiol. 63 (2014) A199.
[33] J.T. Poterucha, S. Kutty, R.K. Lindquist, L. Li, B.W. Eidem, Changes in left ventricular longitudinal strain with anthracycline chemotherapy in adolescents precede subsequent decreased left ventricular ejection fraction, J. Am. Soc. Echocardiogr. 25 (2012) 733–740, http://dx.doi.org/10.1016/j.echo.2012.04.007.
[34] T.C. Tan, S. Bouras, H. Sawaya, I.A. Sebag, V. Cohen, M.H. Picard, J. Passeri, I. Kuter, M. Scherrer-Crosbie, Time trends of left ventricular ejection fraction and myocardial deformation indices in a cohort of women with breast cancer treated with anthracyclines, taxanes, and trastuzumab, J. Am. Soc. Echocardiogr. 28 (2015) 509–514, http://dx.doi.org/10.1016/j.echo.2015.02.001.
[35] H. Sawaya, I.A. Sebag, J.C. Plana, J.L. Januzzi, B. Ky, V. Cohen, S. Gosavi, J.R. Carver, S.E. Wiegers, R.P. Martin, M.H. Picard, R.E. Gerszten, E.F. Halpern, J. Passeri, I. Kuter, M. Scherrer-Crosbie, Early detection and prediction of cardiotoxicity in chemotherapy-treated patients, Am. J. Cardiol. 107 (2011) 1375–1380, http://dx.doi.org/10.1016/j.amjcard.2011.01.006.
[36] H.W. Fei, M.T. Ali, T.C. Tan, K.H. Cheng, L. Salama, L. Hua, X. Zeng, E.F. Halpern, A. Taghian, S.M. MacDonald, M. Scherrer-Crosbie, Left ventricular global longitudinal strain in HER-2+ breast cancer patients treated with anthracyclines and trastuzumab who develop cardiotoxicity is associated with subsequent recovery of left ventricular ejection fraction, Echocardiography 33 (2016) 519–526, http://dx.doi.org/10.1111/echo.13168.
[37] S. Kongbundansuk, W.G. Hundley, Noninvasive imaging of cardiovascular injury related to the treatment of cancer, JACC Cardiovasc. Imaging 7 (2014) 824–838, http://dx.doi.org/10.1016/j.jcmg.2014.06.007.
[38] R.S. Jiji, C.M. Kramer, M. Salerno, Non-invasive imaging and monitoring cardiotoxicity of cancer therapeutic drugs, J. Nucl. Cardiol. 19 (2012) 377–388, http://dx.doi.org/10.1007/s12350-012-9512-2.
[39] F. Bonner, M. Neizel, S. Gruenig, C. Jacoby, M. Kelm, B. Sievers, T2 mapping in different cardiomyopathies: first clinical experience, J. Cardiovasc. Magn. Reson. 15 (2013) P53.
[40] R. Wassmuth, S. Lentzsch, U. Erdbruegger, J. Schulz-Menger, B. Doerken, R. Dietz, M.G. Friedrich, Subclinical cardiotoxic effects of anthracyclines as assessed by magnetic resonance imaging-a pilot study, Am. Heart J. 141 (2001) 1007–1013.
[41] E.B. Tham, M. Haykowsky, K. Chow, M. Spavor, S. Kaneko, N.S. Khoo, J.J. Pagano, A.S. Mackie, R. Thompson, Diffuse myocardial fibrosis by T1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling, J. Cardiovasc. Magn. Reson. 15 (2013) 48, http://dx.doi.org/10.1186/1532-429X-15-48.
[42] C.D. Wiginton, B. Kelly, A. Oto, M. Jesse, P. Aristimuno, R. Ernst, G. Chaljub, Gadolinium-based contrast exposure, nephrogenic systemic fibrosis, and gadolinium detection in tissue, AJR Am. J. Roentgenol. 190 (2008) 1060–1068, http://dx.doi.org/10.2214/AJR.07.2822.
[43] P. Thavendiranathan, A.D. Grant, T. Negishi, J.C. Plana, Z.B. Popović, T.H. Marwick, Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy, J. Am. Coll. Cardiol. 61 (2013) 77–84, http://dx.doi.org/10.1016/j.jacc.2012.09.035.
[44] P. Thavendiranathan, F. Poulin, K.-D. Lim, J.C. Plana, A. Woo, T.H. Marwick, Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review, J. Am. Coll. Cardiol. 63 (2014) 2751–2768, http://dx.doi.org/10.1016/j.jacc.2014.01.073.
[45] A.L. Baggish, K. Yared, F. Wang, R.B. Weiner, A.M. Hutter Jr., M.L. Picard, M.J. Wood, The impact of endurance exercise training on left ventricular systolic mechanics, Am. J. Physiol. Heart Circ. Physiol. 295 (2008) H1109–H1116, http://dx.doi.org/10.1152/ajpheart.00395.
[46] G.-Y. Cho, T.H. Marwick, H.-S. Kim, M.-K. Kim, K.-S. Hong, D.-J. Oh, Global 2-dimensional strain as a new prognosticator in patients with heart failure, J. Am. Coll. Cardiol. 54 (2009) 618–624, http://dx.doi.org/10.1016/j.jacc.2009.04.061.
[47] M. Bertini, A.C.T. Ng, M.L. Antoni, G. Nucifora, S.H. Ewe, D. Auger, N.A. Marsan, M.J. Schalij, J.J. Bax, V. Delgado, Global longitudinal strain predicts long-term survival in patients with chronic ischemic cardiomyopathy, Circ. Cardiovasc. Imaging (2012) 5383–5391, http://dx.doi.org/10.1161/CIRCIMAGING.111.970434.
[48] M. Iacoviello, A. Puzzovivo, P. Guida, C. Forleo, F. Monitillo, R. Catanzaro, M.S. Lattarulo, V. Antoncecchi, S. Favale, Independent role of left ventricular global longitudinal strain in predicting prognosis of chronic heart failure patients, Echocardiography (2013) 803–811, http://dx.doi.org/10.1111/echo.12142.
[49] T. Stanton, R. Leano, T.H. Marwick, Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring, Circ. Cardiovasc. Imaging 2 (2009) 356–364, http://dx.doi.org/10.1161/CIRCIMAGING.109.862334.
[50] J. Lekakis, P. Abraham, A. Balbarini, A. Blann, C.M. Boulanger, J. Cockcroft, F. Cosentino, J. Deanfield, A. Gallino, I. Ikonomidis, D. Kremastinos, U. Landmesser, A. Protogerou, C. Stefanadis, D. Tousoulis, G. Vassalli, H. Vink, N. Werner, I. Wilkinson, C. Vlachopoulos, Methods for evaluating endothelial function: a position statement from the European Society of Cardiology Working Group on peripheral circulation, Eur. J. Cardiovasc. Prev. Rehabil. 18 (2011) 775–789, http://dx.doi.org/10.1177/1741826711398179.
[51] A. Dolci, R. Dominici, D. Cardinale, M.T. Sandri, M. Panteghini, Biochemical markers for prediction of chemotherapy-induced cardiotoxicity systematic review of the literature and recommendations for use, Am. J. Clin. Pathol. 130 (2008) 688–695, http://dx.doi.org/10.1309/AJCPB66LRIIVMQDR.
[52] M. Putt, V.S. Hahn, J.L. Januzzi, H. Sawaya, I.A. Sebag, J.C. Plana, M.H. Picard, J.R. Carver, E.F. Halpern, I. Kuter, J. Passeri, V. Cohen, J. Banchs, R.P. Martin, R.E. Gerszten, M. Scherrer-Crosbie, B. Ky, Longitudinal changes in multiple biomarkers are associated with cardiotoxicity in breast cancer patients treated with doxorubicin, taxanes, and trastuzumab, Clin. Chem. 61 (2015) 1164–1172, http://dx.doi.org/10.1373/clinchem.2015.241232.
[53] K.S. Courneya, R.J. Segal, J.R. Mackey, K. Gelmon, R.D. Reid, C.M. Friedenreich, A.B. Ladha, C. Proulx, J.K. Vallance, K. Lane, Y. Yasui, D.C. McKenzie, Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial, J. Clin. Oncol. 25 (2007) 4396–4404.
[54] K.S. Courneya, D.C. McKenzie, J.R. Mackey, K. Gelmon, C.M. Friedenreich, Y. Yasui, R.D. Reid, D. Cook, D. Jespersen, C. Proulx, L.B. Dolan, C.C. Forbes, E. Wooding, L. Trinh, R.J. Segal, Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial, J. Natl. Cancer Inst. 105 (2013) 1821–1832.
[55] K.S. Courneya, R.J. Segal, D.C. McKenzie, H. Dong, K. Gelmon, C.M. Friedenreich, Y. Yasui, R.D. Reid, J.J. Crawford, J.R. Mackey, Effects of exercise during adjuvant chemotherapy on breast cancer outcomes, Med. Sci. Sports Exerc. 46 (2014) 1744–1751, http://dx.doi.org/10.1249/MSS.0000000000000297.
[56] W.E. Hornsby, P.S. Douglas, M.J. West, A.A. Kenjale, A.R. Lane, E.R. Schwitzer, K.A. Ray, J.E. Herndon II, A. Coan, A. Gutierrez, K.P. Hornsby, E. Hamilton, L.G. Wilke, G.G. Kimmick, J.M. Peppercorn, L.W. Jones, Safety and efficacy of aerobic training inoperable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial, Acta Oncol. 53 (2014) 65–74.
[57] C.J. Kim, D.H. Kang, B.A. Smith, K.A. Landers, Cardiopulmonary responses and adherence to exercise in women newly diagnosed with breast cancer undergoing adjuvant therapy, Cancer Nurs. 29 (2006) 156–165.
[58] M.G. MacVicar, M.L. Winningham, J.L. Nickel, Effects of aerobic interval training on cancer patients' functional capacity, Nurs. Res. 38 (1989) 348–351.
[59] M.J. Haykowsky, J.R. Mackey, R.B. Thompson, L.W. Jones, D.L. Paterson, Adjuvant trastuzumab induces ventricular remodeling despite aerobic exercise training, Clin. Cancer Res. 15 (2009) 4963–4967.
[60] R. Segal, W. Evans, D. Johnson, J. Smith, S. Colletta, J. Gayton, S. Woodard, G. Wells, R. Reid, Structured exercise improves physical functioning in women with stages I and II breast cancer: results of a randomized controlled trial, J. Clin. Oncol. 19 (2001) 657–665.
[61] F. Vincent, J.L. Labourey, S. Leobon, M.T. Antonini, S. Lavau-Denes, N. Tubiana-Mathieu, Effects of a home-based walking training program on cardiorespiratory fitness in breast cancer patients receiving adjuvant chemotherapy: a pilot study, Eur. J. Phys. Rehabil. Med. 49 (2013) 319–329.
[62] N.A. Hutnick, N.I. Williams, W.J. Kraemer, E. Orsega–Smith, R.H. Dixon, A.D. Bleznak, A.M. Mastro, Exercise and lymphocyte activation following chemotherapy for breast cancer, Med. Sci. Sports Exerc. 37 (2005) 1827–1835.
[63] K.S. Courneya, J.R. Mackey, G.J. Bell, L.W. Jones, C.J. Field, A.S. Fairey, Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes, J. Clin. Oncol. 21 (2003) 1660–1668.
[64] A.J. Daley, H. Crank, J.M. Saxton, N. Mutrie, R. Coleman, A. Roalfe, Randomized trial of exercise therapy in women treated for breast cancer, J. Clin. Oncol. 25 (2007) 1713–1721.
[65] B.M. Pinto, G.M. Frierson, C. Rabin, J.J. Trunzo, B.H. Marcus, Home-based physical activity intervention for breast cancer patients, J. Clin. Oncol. 23 (2005) 3577–3587.
[66] C.M. Schneider, C.C. Hsieh, L.K. Sprod, S.D. Carter, R. Hayward, Effects of supervised exercise training on cardiopulmonary function and fatigue in breast cancer survivors during and after treatment, Cancer 110 (2007) 918–925.
[67] Y. Octavia, C.G. Tocchetti, K.L. Gabrielson, S. Janssens, H.J. Crijns, A.L. Moens, Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies, J. Mol. Cell. Cardiol. 52 (2012) 1213–1225, http://dx.doi.org/10.1016/j.yjmcc.2012.03.006.
[68] B. Ky, S.E. Kimmel, R.N. Safa, M.E. Putt, N.K. Sweitzer, J.C. Fang, D.B. Sawyer, T.P. Cappola, Neuregulin-1 beta is associated with disease severity and adverse outcomes in chronic heart failure, Circulation 120 (2009) 310–317, http://dx.doi.org/10.1161/CIRCULATIONAHA.109.856310.
[69] P.J. Perik, E.G. de Vries, J.A. Gietema, W.T. van der Graaf, T.D. Smilde, D.T. Sleijfer, D.J. van Veldhuisen, Serum HER2 levels are increased in patients with chronic heart failure, Eur. J. Heart Fail. 9 (2007) 173–177.
[70] K.R. Chien, Stress pathways and heart failure, Cell 98 (1999) 555–558.
[71] S.A. Crone, Y.Y. Zhao, L. Fan, Y. Gu, S. Minamisawa, Y. Liu, K.L. Peterson, J. Chen, R. Kahn, G. Condorelli, J. Ross Jr., K.R. Chien, K.F. Lee, ErbB2 is essential in the prevention of dilated cardiomyopathy, Nat. Med. 8 (2002) 459–465.
[72] M.J. Haykowsky, Y. Liang, D. Pechter, L.W. Jones, F.A. McAlister, A.M. Clark, A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed, J. Am. Coll. Cardiol. 49 (2007) 2329–2336.
[73] J.M. Scott, S. Lakoski, J.R. Mackey, P.S. Douglas, M.J. Haykowsky, L.W. Jones, The potential role of aerobic exercise to modulate cardiotoxicity of molecularly targeted cancer therapeutics, Oncologist 18 (2013) 221–223, http://dx.doi.org/10.1634/theoncologist.2012-0226.
[74] K.Y. Wonders, B.S. Reigle, Trastuzumab and doxorubicin-related cardiotoxicity and the cardioprotective role of exercise, Integr. Cancer Ther. 8 (2009) 17–21, http://dx.doi.org/10.1177/1534735408330717.
[75] C.G. Lenneman, D.B. Sawyer, Cardio-oncology: an update on cardiotoxicity of cancer-related treatment, Circ. Res. 118 (2016) 1008–1020, http://dx.doi.org/10.1161/CIRCRESAHA.115.303633.
[76] U. Wisløff, Ø. Ellingsen, O.J. Kemi, High-intensity interval training to maximize cardiac benefits of exercise training? Exerc. Sport Sci. Rev. 37 (2009) 139–146, http://dx.doi.org/10.1097/JES.0b013e3181aa65fc.

[77] U. Wisløff, A. Støylen, J.P. Loennechen, M. Bruvold, O. Rognmo, P.M. Haram, A.E. Tjønna, J. Helgerud, S.A. Slørdahl, S.J. Lee, V. Videm, A. Bye, G.L. Smith, S.M. Najjar, O. Ellingsen, T. Skjaerpe, Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study, Circulation 115 (2007) 3086–3094.
[78] D.S. Hydock, C.Y. Lien, C.M. Schneider, R. Hayward, Exercise preconditioning protects against doxorubicin-induced cardiac dysfunction, Med. Sci. Sports Exerc. 40 (2008) 808–817, http://dx.doi.org/10.1249/MSS.0b013e318163744a.
[79] K.M. Sturgeon, B. Ky, J.R. Libonati, K.H. Schmitz, The effects of exercise on cardiovascular outcomes before, during, and after treatment for breast cancer, Breast Cancer Res. Treat. 143 (2014) 219–226, http://dx.doi.org/10.1007/s10549-013-2808-3.
[80] J.M. Scott, A. Khakoo, J.R. Mackey, M.J. Haykowsky, P.S. Douglas, L.W. Jones, Modulation of anthracycline-induced cardiotoxicity by aerobic exercise in breast cancer: current evidence and underlying mechanisms, Circulation 124 (2011) 642–650, http://dx.doi.org/10.1161/CIRCULATIONAHA.111.021774.
[81] A. Ascensao, J. Lumini-Oliveira, N.G. Machado, R.M. Ferreira, I.O. Gonçalves, A.C. Moreira, F. Marques, V.A. Sardão, P.J. Oliveira, J. Magalhães, Acute exercise protects against calcium-induced cardiac mitochondrial permeability transition pore opening in doxorubicin-treated rats, Clin. Sci. (Lond.) 120 (2011) 37–49, http://dx.doi.org/10.1042/CS20100254.
[82] A. Ascensão, J. Magalhães, J.M. Soares, R. Ferreira, M.J. Neuparth, F. Marques, P.J. Oliveira, J.A. Duarte, Moderate endurance training prevents doxorubicin-induced in vivo mitochondriopathy and reduces the development of cardiac apoptosis, Am. J. Physiol. Heart Circ. Physiol. 289 (2005) H722–H731.
[83] A.N. Kavazis, A.J. Smuder, K. Min, N. Tümer, S.K. Powers, Short-term exercise training protects against doxorubicin-induced cardiac mitochondrial damage independent of HSP72, Am. J. Physiol. Heart Circ. Physiol. 299 (2010) H1515–H1524, http://dx.doi.org/10.1152/ajpheart.00585.2010.
[84] A. Ascensão, J. Magalhães, J. Soares, R. Ferreira, M. Neuparth, F. Marques, J. Oliveira, J. Duarte, Endurance training attenuates doxorubicin-induced cardiac oxidative damage in mice, Int. J. Cardiol. 100 (2005) 451–460.
[85] A.J. Chicco, C.M. Schneider, R. Hayward, Voluntary exercise protects against acute doxorubicin cardiotoxicity in the isolated perfused rat heart, Am. J. Physiol. Regul. Integr. Comp. Physiol. 289 (2005) R424–R431.
[86] K.Y. Wonders, D.S. Hydock, C.M. Schneider, R. Hayward, Acute exercise protects against doxorubicin cardiotoxicity, Integr. Cancer Ther. 7 (2008) 147–154, http://dx.doi.org/10.1177/1534735408322848.