Carnitine Deficiency Disorders in Pediatrics

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Anthracycline-Induced Cardiotoxicity in Young Cancer Patients: The Role of Carnitine

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Key Words
Carnitine · Childhood cancer · Anthracyclines · Cardiomyopathy · Prevention

Abstract
While the increased rates of survival in childhood cancers have increased progressively in recent decades, many childhood cancer survivors will have at least one chronic health condition within 40 years of age. In this regard, cardiovascular complications have emerged as a leading cause of long-term morbidity and mortality in long-term survivors of childhood cancer, likely due to exposure to anthracycline chemotherapy, and outcomes in patients with anthracycline-related cardiomyopathy remain poor. Some progress has been made in understanding the mechanisms at the basis of anthracycline-related cardiomyopathy, which appear to involve generation of reactive oxygen species, leading to mitochondrial dysfunction, followed by myocyte apoptosis and maladaptive left ventricular remodeling. Even if several guidelines currently exist for monitoring cancer patients treated with cardiotoxic therapies who are at high risk for heart failure, much work remains to be done in finding reliable markers for screening for cardiac dysfunction. Studies from our group have identified alterations in L-carnitine in cancer survivors. While additional investigations are needed, preliminary studies suggest a role for carnitine in primary prevention (during treatment) and secondary prevention (to improve function after treatment). © 2016 S. Karger AG, Basel

Survival rates in childhood cancers have increased both steadily in recent decades [1]. In fact, cure is now the most probable outcome for children and adolescents diagnosed with cancer. While 5-year survival rates were around 60–70% in the 1970s and 1980s, they have now increased to at least 80%. However, the increased survival rates are also accompanied by a downside, namely that many of these childhood cancer survivors will have at least one chronic health condition within 40 years of age. According to the data from The Childhood Cancer Survivor Study, 62.3% of individuals had at least one chronic condition and 27.5% had a condition that was classified as life-threatening or severe [2].

Cardiovascular Disease in Childhood Cancer Survivors

Cardiovascular complications have emerged as a leading cause of long-term morbidity and mortality in long-term survivors of childhood cancer. In fact, compared to

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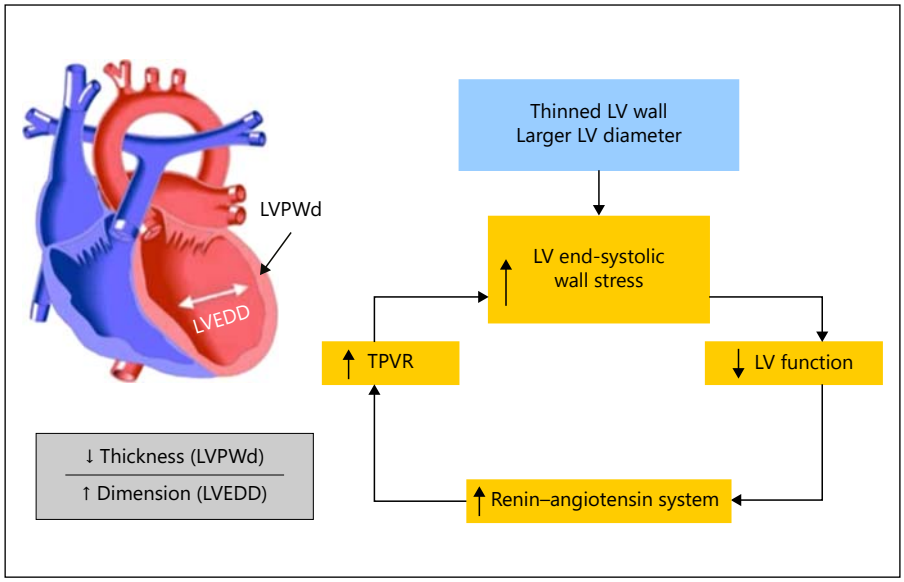

Fig. 1. Depiction of chronic left ventricular (LV) remodeling following treatment with anthracyclines. LVPWd = LV posterior wall thickness in diastole; LVEDD = LV end-diastolic dimension.

their siblings, these survivors have a 9–15-fold increased risk of developing stroke, heart attacks and heart failure [2]. There is often a long latency between cancer treatment and onset of cardiovascular disease, making it especially challenging to study cardiovascular late effects in this population. These limitations notwithstanding, studies in childhood cancer survivors over the past 3 decades have found a strong association between certain therapeutic exposures such as anthracycline chemotherapy (e.g., doxorubicin, daunorubicin, epirubicin, idarubicin) and cardiovascular complications such as cardiomyopathy or heart failure.

Anthracyclines were discovered in the 1960s and have since become a mainstay of cancer treatment; more than half of children diagnosed with cancer will receive treatment with an anthracycline. As is well known, cardiotoxicity is a dose-limiting factor for anthracyclines, and following their administration, there is a variable period of asymptomatic cardiomyopathy. The period of asymptomatic cardiomyopathy can vary greatly, with acute events being rare and late occurring events being more common. A clear dose–response relationship has been shown between cumulative anthracycline exposure and risk of cardiomyopathy, and there is a high risk that these develop at an early age; modifiers of risk include female gender, younger age and chest radiation [3].

Unfortunately, outcomes in patients with anthracycline-related cardiomyopathy are especially poor compared to those with cardiomyopathy due to ischemic heart disease, idiopathic cardiomyopathy or peripartum cardiomyopathy [4]. As such, it is especially important to understand the biologic and physiologic processes that drive cardiomyopathy risk, so that proper interventions can be implemented to avert the onset of clinically overt heart failure and depiction of cancer treatment-related decline in cardiac function.

Mechanisms of Anthracycline-Induced Cardiomyopathy

Regarding the mechanisms at the basis of anthracycline-related cardiomyopathy, it would appear that the generation of reactive oxygen species leads to mitochondrial dysfunction, followed by myocyte apoptosis and maladaptive left ventricular (LV) remodeling [5]. Chronic LV remodeling is characterized by decreased LV posterior wall thickness and decreased LV end diastolic diameter, resulting in upregulation of the renin–angiotensin system, and compensatory increase in total peripheral vascular resistance (fig. 1).

In addition, cardiac abnormalities have been found to be persistent and progressive after doxorubicin therapy. Inadequate ventricular mass with chronic afterload excess is associated with progressive contractile deficit and possibly reduced cardiac output and restrictive cardiomyopathy [5]. While such deficits appeared to be worse following the highest cumulative doses of doxorubicin, they nonetheless can be present even after low doses [6].

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Monitoring Recommendations

The American College of Cardiology/American Heart Association guidelines consider cancer patients treated with cardiotoxic therapies such as anthracyclines at high risk for heart failure [7]. In fact, the Children's Oncology Group has issued long-term follow-up guidelines that recommend routine echocardiographic screening (range: annual to every 5 years) for survivors treated with anthracyclines, so that cardiac dysfunction can be detected prior to onset of symptomatic and irreversible disease [8]. In considering possible early treatments of anthracycline-induced cardiomyopathy, one study has shown that in doxorubicin-treated long-term survivors of childhood cancer, enalapril induced transient improvement in LV structure and function. However, the primary defect, namely LV wall thinning, continues to deteriorate [9].

Screening for Cardiac Dysfunction

It is obvious that greater effort needs to be given to early screening and detection of cardiac dysfunction in survivors of childhood cancers who received anthracyclines. In a recent study, the utility and reliability of obtaining early echocardiographic measurements of LV remodeling as well as blood biomarkers of cardiac injury in asymptomatic childhood cancer survivors at risk for LV dysfunction and heart failure due to past exposure to anthracycline chemotherapy were investigated [10]. It was found that cancer survivors with preserved ejection fraction at >10 years from anthracycline exposure had dose-dependent changes in echocardiographic markers of LV dysfunction. However, with the exception of NT-proBNP, there was no correlation between blood biomarkers (B-type natriuretic peptide, troponin-T, ST-2, galectin-3) and LV dysfunction.

Metabolomics Analysis

Our laboratory has also undertaken metabolomics analysis, or comprehensive profile of small-molecule metabolites, in 150 asymptomatic childhood cancer survivors previously treated with anthracyclines in 8 pathways for a total of 354 metabolites [11]. Plasma levels of 15 compounds in 3 metabolic pathways (carbohydrate, amino acid and lipid metabolism) were found to be significantly different between individuals with cardiac dysfunction and those with normal systolic function (table 1).

Identification of L-Carnitine Alterations in Cancer Survivors

After adjusting for multiple comparisons, individuals with cardiac dysfunction had significantly lower plasma carnitine levels and higher levels of essential and long-chain fatty acids (LCFA) than those with normal systolic function. This is relevant as LCFA are a major substrate for energy production in myocardium, and transport of LCFA rate limiting step in fatty acid oxidation. Moreover, cardiac myocytes contain relatively high concentrations of carnitine. Carnitine is actively transported into the cell, since myocytes are incapable of carnitine biosynthesis [12, 13]. Clinically, both primary and secondary carnitine deficiency has been shown to result in cardiomyopathy and cardiac arrhythmias, due in part to the accumulation of LCFA and acylcarnitines that cannot be oxidized in the mitochondria, and thus are unavailable for energy production [12, 14]. Interestingly, in patients with a past history of myocardial infarction, administration of L-carnitine has been shown to lead to attenuation of LV dilation, prevent LV remodeling and was associated with a lower incidence of chronic heart failure and cardiac death [15].

Anthracyclines and L-Carnitine

Previous studies have suggested that anthracyclines may exert at least part of their cardiotoxicity by inhibiting LCFA oxidation in the heart. In a rat model of anthracycline-induced cardiotoxicity, doxorubicin treatment was associated with a dose-dependent increase in the expression of the apoptotic genes *P53* and *CD95* [16]. In addition, carnitine supplementation restored doxorubicin-induced inhibition of gene expression of *H-FABP* and *OCTN2*, and led to a decrease in myocardial carnitine control values. While there has been some concern that the addition of carnitine to a chemotherapy regimen containing an anthracycline may alter its efficacy, supplementation with L-carnitine was not found to reduce the efficacy of epirubicin treatment in breast cancer cells [17]. This suggests that supplementation with L-carnitine in patients undergoing epirubicin treatment might be used to reduce associated cardiotoxicities.

In a meta-analysis of carnitine and prevention of cardiovascular disease, compared with placebo or control, L-carnitine was associated with a 27% reduction in all-cause mortality, a 65% reduction in ventricular arrhythmias and a 40% reduction in anginal symptoms in pa-

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Table 1. Plasma metabolites altered in anthracycline-exposed childhood cancer survivors with cardiac dysfunction

Pathway	Biochemical name	Relative ratio (abnormal: normal)	p value	Q value
Tryptophan	C-glycosyltryptophan	1.16	0.001	0.061
Carbohydrate	Mannose	1.13	0.005	0.190
Carbohydrate	Threitol	1.11	0.009	0.091
Carbohydrate	Gluconate	1.17	0.015	0.117
Essential fatty acid	Di-homo-linolenate	1.27	0.008	0.049
Essential fatty acid	Eicosapentaenoate	1.23	0.006	0.050
Essential fatty acid	Docosapentaenoate	1.46	<0.001	0.032
Medium chain fatty acid	Caproate	1.19	0.016	0.221
LCFA	Stearidonate	1.20	0.050	0.212
LCFA	Docosadienoate	1.26	0.003	0.042
LCFA	Adrenate	1.29	0.004	0.040
Carnitine	Carnitine	0.88	0.002	0.034
Bile acid	Glycocholenate	0.80	0.009	0.089
Glycerolipid	Choline	1.04	0.044	0.202
Lysolipid	1-Stearoylglycerophosphoinositol	1.46	0.001	0.058
Lysolipid	1-Arach idonoylglycerophosphoinositol	1.15	0.036	0.203
Steroid/sterol	Dehydroisoandrosterone sulfate	0.59	0.02	0.172
Steroid/sterol	4-Androsten-3beta,17beta-diol disulfate 2	0.72	0.044	0.223
Steroid/sterol	Andro steroid monosulfate 2	0.61	0.001	0.071
Steroid/sterol	4-Androsten-3beta,17beta-diol disulfate 1	0.91	0.032	0.108

tients experiencing an acute myocardial infarction [18]. Those authors concluded that large randomized controlled trials of L-carnitine are thus warranted.

Future Directions

In considering such trials, it is useful to note that exercise-spiroergometry and stress-echocardiography have been used to diagnose anthracycline-induced late cardiomyopathy [19]. This relatively inexpensive tool might be incorporated into any future clinical trials as it can also provide information for therapeutic prevention before the appearance of clinical symptoms of cardiomyopathy that may not be revealed by other methods.

Together, these findings may facilitate the development of primary prevention (treatment of carnitine deficiency before/during anthracycline administration) and secondary prevention strategies (screening and treatment in long-term survivors) in childhood cancer survivors who are at risk for anthracycline-related cardiomyopathy. While the etiology and timing/onset of depletion is unclear, preliminary studies suggest a role for carnitine in primary prevention (during treatment) and secondary prevention (to improve function after treatment).

Conclusions

- Childhood cancer survivors are at risk for treatment-related cardiomyopathy.

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- Cardiomyopathy may be associated with relative carnitine depletion.
  - The etiology and timing/onset of depletion is unclear.
- Preliminary studies suggest a role for carnitine in:
  - Primary prevention (during treatment).
  - Secondary prevention (to improve function after treatment).
- In non-cancer populations, carnitine has been shown to have a potential role in both primary and secondary prevention of cardiovascular disease.

Disclosure Statement

S.H.A. has no conflicts to report.

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