Eur J Pediatr
DOI 10.1007/s00431-012-1849-7

ORIGINAL ARTICLE

Myocardial function in children after fetal chemotherapy exposure. A tissue Doppler and myocardial deformation imaging study

Mina Mhallem Gziri · Wei Hui · Frédéric Amant · Kristel Van Calsteren · Nelleke Ottevanger · Livia Kapusta · Luc Mertens

Received: 11 July 2012 / Revised: 19 September 2012 / Accepted: 22 September 2012

Abstract Chemotherapy and particularly anthracycline exposure are associated with acute and chronic cardiotoxicity. Few data exist on the effect of cardiac function after in utero exposure to maternal chemotherapy. Our recently published multicenter prospective study showed no significant changes in systolic function using conventional echocardiographic parameters. The purpose of this study was to further investigate whether early functional changes can be detected using tissue Doppler imaging (TDI) and two-dimensional (2D) speckle tracking echocardiography (STE). Sixty-two children (median/range age 1.7 (1–9.8)years) exposed to chemotherapy during fetal life were enrolled and compared to 62 age- and gender-matched controls. TDI velocities were measured at the basal interventricular septum (IVS) and right and left ventricular (LV) free walls. LV global longitudinal and circumferential systolic strains were derived using 2D STE. We found small but significant differences between the groups (patients versus controls) in LV fractional shortening [35 (29–46)% versus 39 (28–53)%, $p<0.001$], LV ejection fraction [66 (57–79)% versus 70 (57–83)%, $p<0.001$], LV posterior wall thickness z score [−0.15 (−2.32–1.81) versus −0.10 (−1.9–2.0), $p<0.001$], and IVS thickness z score [−1.06 (−2.6–1.3) versus −0.5 (−2.1–1.7), $p<0.001$]. No significant differences in TDI velocities or LV global strains were observed. Within the patient group, the cardiac functional parameters did not correlate to the number of cycles of anthracycline or the cumulative anthracycline dose. Children exposed to fetal chemotherapy have a lower normal fractional shortening and mildly lower left ventricular wall thickness. Tissue Doppler and strain measurements are within normal range and not statistically different from normal controls. The long-term implications of these findings will be further studied in this prospective cohort study.

Keywords Children · Fetal chemotherapy · Myocardial function · Speckle tracking · Tissue Doppler imaging

Mina Mhallem Gziri and Wei Hui contributed equally to this manuscript.

M. M. Gziri · F. Amant
Leuven Cancer Institute, University Hospitals Leuven,
Katholieke Universiteit Leuven,
Leuven, Belgium

W. Hui · L. Mertens
Division of Cardiology, The Hospital for Sick Children,
The University of Toronto,
Toronto, ON, Canada

K. Van Calsteren
Feto-maternal Unit, University Hospitals Leuven,
Leuven, Belgium

N. Ottevanger · L. Kapusta
Radboud University Nijmegen Medical Centre,
Nijmegen, The Netherlands

L. Kapusta
Wolfson Medical Center,
Holon, Israel

L. Mertens (✉)
The Labatt Family Heart Center, The Hospital for Sick Children,
555 University Avenue,
Toronto M5G 1X8, Canada
e-mail: luc.mertens@sickkids.ca

Abbreviations

2D	Two dimensional
BSA	Body surface area
IVS	Interventricular septum
IVRT	Isovolumetric relaxation time
LV	Left ventricle
LVEDD	Left ventricular end-diastolic diameter

Published online: 05 October 2012

RV	Right ventricle
RVEDD	Right ventricular end-diastolic diameter
LVPW	Left ventricle posterior wall
FS	Fractional shortening
EF	Ejection fraction
STE	Speckle tracking echocardiography
TDI	Tissue Doppler imaging

Introduction

Cancer during pregnancy occurs in around 1/1,000–2,000 pregnancies [1]. Maternal cancer treatment can be required during pregnancy and beyond the first trimester, chemotherapy can be administered. This exposes the fetus to potential cardiotoxic and neurotoxic effects of chemotherapeutic agents [2]. Particularly anthracyclines are known for their cardiotoxic side effects which can result in cardiac dysfunction and cardiomyopathy, even many years after the initial exposure [3, 4]. Anthracyclines are part of the standard treatment of different types of breast and blood cancers, the two most common malignancies diagnosed during pregnancy. Recent retrospective studies have suggested that the outcomes for fetuses exposed to maternal chemotherapy is excellent but no good prospective data are available [5–8]. Our group performed a prospective multicenter study investigating the cardiac effects of cancer treatment during pregnancy [9]. When using standard echocardiographic measurements, the patient group exposed to maternal chemotherapy showed a mildly lower but normal ejection fraction and fractional shortening compared to normal controls. The clinical significance of this finding is however still uncertain. Recent data have suggested that tissue Doppler imaging (TDI) and two-dimensional (2D) speckle tracking echocardiography (STE) can be useful for detecting subclinical cardiac dysfunction in patients exposed to anthracyclines prior to changes in ejection fraction [10–13]. Tissue Doppler measures the velocity at which myocardial segments move during the cardiac cycle [14]. Annular velocities of the mitral and tricuspid annulus reflect longitudinal shortening of the left ventricle (LV) and right ventricle (RV) walls and provide additional information on ventricular function. As tissue Doppler velocities in one segment can be influenced by the function of adjacent segments and because the heart moves within the chest during the cardiac cycle, myocardial velocities do not accurately reflect regional myocardial function. To overcome this limitation myocardial deformation imaging or strain imaging was developed to assess regional and global myocardial stain [15]. Strain is a dimensionless unit reflecting the amount of myocardial shortening in systole in the longitudinal and circumferential direction. Strain imaging has been shown to add useful additional information on myocardial function also in the pediatric age range. The aim of the current study was to assess cardiac performance in children exposed to fetal chemotherapy using TDI and STE.

Methods

Study group

A total of 62 children from Belgium and the Netherlands were included between March 2005 and February 2012. Forty-nine children (TDI and images for STE available) were included from our previous study [9]. We recruited 13 additional children between March 2011 and March 2012. All patients had been exposed to chemotherapy in utero and obstetrical data were also recorded. The patient group was compared with an age- and gender-matched control group. The control subjects were recruited from normal healthy volunteers or were children referred for a cardiac murmur found to have a structurally and functionally normal heart. In the normal control group 34 (54.8 %) were recruited in Toronto and 28 (45.2 %) in Belgium. The local ethical committees at the recruiting sites approved the study and informed consent was obtained prior to the research echocardiographic studies.

Echocardiographic measurements

All echocardiograms were performed using a Vivid 7 machine (GE Vingmed Ultrasound, Horten, Norway) using a S4, S5, or S7 transducer, depending on the patient's age and size. A standardized echocardiographic protocol was followed. Data were digitally stored and transferred to the core laboratory for centralized analysis (Research Echocardiography Laboratory, The Hospital for Sick Children, Toronto). Measurements were performed using the EchoPAC version 7.0 workstation (GE Healthcare, USA) by a single experienced research sonographer. Measurements of cardiac dimensions were converted into z scores based on the normative dataset generated at The Hospital for Sick Children in Toronto.

Color tissue Doppler images were acquired from the apical four-chamber view (frame rate between 150 and 250 frames per second). Tissue Doppler velocity curves were obtained at the basal segments of the LV lateral wall, the interventricular septum (IVS), and the right ventricular (RV) free wall, just below the annulus. Systolic, early diastolic, and late diastolic peaks were measured. Measurements from three cardiac cycles were averaged. Optimal alignment of the Doppler beam with the wall motion was defined within 15°. Those acquisitions without optimal alignment were excluded from the final analysis. Our group studied the intra and interobserver variability of this method

which was proven to be low and acceptable for echocardiographic measurements [16].

Grayscale images for offline speckle-tracking analysis were acquired at frame rates between 50 and 90 frames per second. Analysis was performed as described by our group [10]. LV circumferential strain was measured from the parasternal short-axis view at mid-ventricular level (showing both papillary muscles). Peak systolic strain was measured in the anterior, anterolateral inferolateral, inferior, inferoseptal, and anteroseptal segments. Mean circumferential strain was calculated as the mean value of the six segmental measurements. Longitudinal strain was calculated as the mean value of the six segmental measurements. Longitudinal strain was measured from apical four-chamber view in the basal, mid and apical septal, and lateral wall segments. Tracking was automatically performed, and the analysis was accepted after visual inspection and when the software indicated adequate tracking. If tracking was suboptimal, the endocardial border was retraced. If satisfactory tracking was not accomplished after three retracings, the non-tracking segments were excluded from analysis. If more than three of six (inclusive) segments had poor tracking, the study was excluded. Our group studied the validity of the speckle-tracking measurements and showed that global longitudinal and circumferential strain measurements were highly reproducible with low intra- and inter-observer variability [17].

Statistical analysis

All results were expressed in median with range. Mann–Whitney tests were used to test the difference of echo measurements as well as their z scores between patient group and control group. The Spearman's rank coefficient was calculated to evaluate the correlation between the number of chemotherapy cycles and cardiac performance within the anthracycline group. Statistical analyses were performed using the Prism 5 software (GraphPad Software, Inc, La Jolla, CA, USA). A p value <0.05 was considered significant.

Results

Patient characteristics

The study group consisted of 62 children exposed to chemotherapy in utero during 60 pregnancies (two twin pregnancies). The median age of the patient group was 1.7 years old (range 1 to 9.8). Thirty-six were male and 26 female. The diagnosed maternal malignancies included breast cancer (n=33, 55 %), hematological (n=14, 23.3 %), cervix cancer (n=5, 8.3 %), ovarian cancer (n=4, 6.7 %), nasopharyngeal cancers (n=1, 1.68 %), Ewing sarcoma (n=1, 1.68 %), brain tumor (n=1, 1.68 %), and colon tumor (n=1, 1.68 %). Cancer was treated by chemotherapy alone in 40.3 %, by chemotherapy and surgery in 53.2 %, or by chemotherapy and radiotherapy in 6.5 %. Chemotherapy was started at a median gestational age of 23 weeks (14 to 33 weeks) and 1 up to 7 cycles of chemotherapy (median, 4 cycles) were administered during pregnancy. Forty-nine children were exposed to anthracyclines alone or with other chemotherapeutic agents (cyclophosphamide, 5-fluorouracil, methotrexate, bleomycine, vinblastine, dacarbazine, procarbazine, vincristine, rituximab, and oncovin). Thirteen children were exposed to chemotherapy other than anthracyclines agents (cisplatinum, 5-fluorouracil, cyclophosphamide, methotrexate, etoposide, bleomycine, carboplatinum, and paclitaxel). Children data are summarized in the study profile (Table 1). Data on anthracyclines types and doses are summarized in Table 2.

Conventional echocardiographic data

Table 3 summarizes the standard echocardiographic findings. The patients and controls were matched for age, sex, and body surface area (BSA). The patients had a slightly higher systolic and diastolic blood pressure. The LV fractional shortening (FS) and ejection fraction (EF) were statistically lower (p<0.001) in the patient group. No patient was diagnosed with an abnormal FS or EF defined as FS

Table 1 Study profile

	Children (n=62)
Gestational age at delivery (weeks)	35.7 (range, 28.5 to 40.9)
Birthweight (grams)	2,585 (range, 720 to 3,970)
Prematurity (before 37 weeks)	41 children (66.2 %)
Malformations	6 children (9.7 %)
	Double cartilage ring in both ears
	Pectus excavatum
	Bilateral partial syndactily digiti II–III
	Bilateral small protuberance on phalanx-5
	Hip subluxation
	Rectal atresia
Age at examination (years)	1 year, 2 children
	18 months, 29 children
	2 years, 6 children
	3–4 years, 3 children
	7 years, 3 children
	8–9 years, 9 children
Body surface area (m^2)	0.56 (range, 0.37 to 1.25)
Exposure to antharacyclines	49 (79 %) but data available for 43 patients (69.4 %)

Table 2 Anthracyclines types and doses (n=43), data expressed as median ± range

Type of anthracyclines	Number of chemotherapy cycles	Cumulative dose (milligrams) administered during pregnancy
Idarubicin (1)	4±0	35.2±0
Daunorubicin (2)	2±0	272.7±0
Epirubicin (14)	5 (range, 2 to 6)	554 (range, 300 to 1,200)
Doxorubicin (26)	4 (range, 1 to 8)	313 (range, 65.5 to 630)

<28 % or EF <57 %. The z scores for the interventricular septum thickness and left ventricle posterior wall (LVPW) thickness were significantly lower in patient group (p<0.05). Eight patients (median age 6.3 years; range 1.5 to 9.4 years) had an IVS thickness z score below −2 (−2.1 to −2.6). Five of the eight patients with abnormal IVS z score had been exposed to anthracyclines. The other three were exposed to cisplatinum for maternal cervical cancer. Only two patients were diagnosed with LVPW thickness z scores <2.0. Both had been exposed to anthracyclines. Interestingly, the values for IVS and LVPW thickness uncorrected for BSA were not different between the two groups.

Comparison of patients and controls using speckle tracking and TDI

Table 4 summarizes the tissue Doppler and the strain measurements. From the color tissue Doppler acquisition, we could obtain good alignment and reliable velocity traces in 56 patients (90.4 %) and in 57 control children (91.4 %) for the LV lateral wall, 54 patients (86.9 %) and 54 controls (86.9 %) for the RV free wall, and in 57 patients (91.4 %) and in 59 control children (95.2 %) for the IVS. No significant differences in tissue Doppler velocities values were noted between the patients and the normal controls.

Mean longitudinal strain measurements could be obtained in 46 control patients (74 %) and in 59 of the fetal chemotherapy group (95.2 %). Mean LV global circumferential strain was obtained in 55 of the fetal group (88.7 %) and in 57 (91.4 %) controls. There were no significant differences in longitudinal and circumferential strain measurements (Table 4).

Comparison between patients exposed to fetal anthracyclines and controls

We further compared the patients who had been exposed to anthracyclines (n=49) to the control group (Table 5). Children exposed to anthracyclines had a higher diastolic blood pressure but remains between normal ranges. The patient group had a significant lower FS, EF, and IVS thickness compared to the control group. We also further explored whether patients who were exposed to anthracyclines during fetal life were different from patients who were not treated with anthracyclines. The data are summarized in Table 6. We found no significant differences in conventional cardiac measurements, TDI velocities, and strain measurements between the two subgroups. No significant

Table 3 Conventional echocardiography in patients with exposure to chemotherapy in utero and normal controls

Value	Patient (n=62)	Controls (n=62)	p values
Age (year)	1.7 (1 to 9.8)	2 (0.7 to 9.5)	0.98
Male/female	36/26	36/26	1.00
Body surface area (m^2)	0.56 (0.42 to 1.38)	0.56 (0.37 to 1.25)	0.46
Systolic blood pressure (mmHg)	104 (82 to 131)	96 (74 to 115)	0.013
Diastolic blood pressure (mmHg)	63 (48 to 78)	55 (40 to 85)	<0.001
Heart rate (beats/min)	110 (57 to 152)	106 (54 to 146)	0.47
LV shortening fraction (%)	35 (29 to 46)	39 (28 to 53)	<0.001
LV ejection fraction (%)	66 (57 to 79)	70 (57 to 83)	<0.001
LVEDD (cm)	3.10 (2.30 to 4.50)	3.12 (2.40 to 4.70)	0.66
LVEDD z score	−0.10 (−2.36 to 3.19)	0.10 (−2.20 to 3.00)	0.17
RVEDD (cm)	1.40 (0.93 to 2.20)	1.40 (0.90 to 2.26)	0.86
RVEDD z score	0.70 (−1.50 to 2.10)	0.40 (−1.90 to 2.20)	0.47
LVPW thickness (cm)	0.42 (0.29 to 0.70)	0.46 (0.3 to 0.74)	0.08
LVPW thickness z score	−0.15 (−2.32 to 1.81)	−0.10 (−1.90 to 2.00)	0.034
IVS thickness (cm)	0.40 (0.34 to 0.60)	0.40 (0.30 to 0.66)	0.27
IVS thickness z score	−1.06 (−2.62 to 1.30)	−0.50 (−2.10 to 1.70)	0.001
Mitral Doppler E/A ratio	1.64 (1.03 to 2.63)	1.66 (0.92 to 3.37)	0.21
IVRT (ms)	48 (30 to 85)	51 (37 to 85)	0.002

Table 4 TDI measurements and mean strain values

	Study patients (n=62)	Controls (n=62)	p values
TDI basal segment LV lateral wall			
Peak systolic velocity (cm/s)	5.3 (2.9 to 10.0)	5.7 (2.6 to 9.0)	0.75
Peak early diastolic velocity (cm/s)	−11.2 (−3.5 to −16.1)	−10.1 (−3.6 to −15.9)	0.44
Peak late diastolic velocity (cm/s)	−3.9 (−0.94 to −10.4)	−3.4 (−1.1 to −12.6)	0.45
TDI basal segment IVS			
Peak systolic velocity (cm/s)	5.9 (4.3 to 8.4)	5.9 (3.3 to 7.8)	0.97
Peak early diastolic velocity (cm/s)	10.6 (4.2 to 15.6)	9.6 (5 to 13.9)	0.08
Peak late diastolic velocity (cm/s)	4.8 (0.61 to 10.2)	4.7 (1.4 to 14.8)	0.85
TDI basal segment RV lateral wall			
Peak systolic velocity (cm/s)	10.3 (7.3 to 15.4)	10.0 (4.0 to 15.1)	0.29
Peak early diastolic velocity (cm/s)	−12.7 (−6.9 to −22.4)	−11.7 (−7.2 to −19.4)	0.11
Peak late diastolic velocity (cm/s)	−8.4 (−2.7 to −14.7)	−7.2 (−1.6 to −19.1)	0.08
Mean LV longitudinal strain (%)	19 (13 to 27)	21 (13 to 26)	0.19
Mean LV circumferential strain (%)	20 (10 to 26)	19 (19 to 24)	0.72

correlations could be found between the cardiac functional parameters and the number of chemotherapy cycles or the cumulative dose of doxorubicin and epirubicin (data not shown).

Table 5 Comparing patients with anthracyclines exposure in utero to the control group

	Anthracyclines (49)	Control group (49)	p values
Age (years)	1 (1.8 to 9.8)	2.1 (0.7 to 9.5)	0.95
BSA (m^2)	0.56 (0.42 to 1.38)	0.56 (0.37 to 1.25)	0.44
Heart rate (beats/min)	109 (57 to 147)	105 (54 to 146)	0.71
Systolic blood pressure (mmHg)	100 (82 to 115)	97 (74 to 115)	0.29
Diastolic blood pressure (mmHg)	60 (48 to 77)	54 (40 to 85)	0.002
LV shortening fraction (%)	35 (29 to 46)	38.5 (28 to 53)	<0.001
LV ejection fraction (%)	66 (57 to 79)	70 (57 to 80)	<0.001
LVEDD (cm)	3.10 (2.50 to 4.50)	3.10 (2.40 to 4.70)	0.89
LVEDD z score	0.22 (−2.00 to 3.19)	0.15 (−2.20 to 3.00)	0.29
RVEDD (cm)	1.40 (0.93 to 2.20)	1.40 (0.90 to 2.26)	0.53
RVEDD z score	0.72 (−1.50 to 2.10)	0.30 (−1.90 to 2.20)	0.39
LVPW thickness	0.42 (0.29 to 0.7)	0.47 (0.10 to 0.74)	0.14
LVPW thickness z score	−0.07 (−2.32 to 1.81)	−0.22 (−1.9 to 2.00)	0.08
IVS thickness	0.40 (0.34 to 0.60)	0.42 (0.30 to 0.67)	0.60
IVS thickness z score	−0.96 (−2.50 to 1.30)	−0.40 (−2.10 to 1.70)	0.013
Mitral Doppler E/A ratio	1.7 (1.2 to 2.6)	1.7 (1.1 to 3.4)	0.24
IVRT (ms)	44 (32 to 81)	51 (38 to 79)	<0.001
LV mean longitudinal strain (%)	20 (13 to 27)	21 (13 to 26)	0.84
LV mean circumferential strain (%)	20 (10 to 26)	19 (13 to 24)	0.49
LV TDI velocity S′ (cm/s)	5.3 (2.9 to 10.0)	5.3 (2.6 to 8.9)	0.89
LV TDI velocity E′ (cm/s)	−11.0 (−3.5 to −15.7)	−10.2 (−3.6 to −15.9)	0.60
LV TDI velocity A′ (cm/s)	−3.8 (−1.0 to −10.4)	−3.6 (−1.1 to −12.6)	0.99
IVS TDI velocity S′ (cm/s)	5.9 (4.8 to 8.4)	5.9 (3.3 to 7.2)	0.55
IVS TDI velocity E′ (cm/s)	−10.3 (−6.7 to −14.7)	−9.6 (−5.0 to −12.6)	0.08
IVS TDI velocity A′ (cm/s)	−4.6 (−0.7 to −10.2)	−4.6 (−1.6 to −14.8)	0.84
RV TDI velocity S′ (cm/s)	10.0 (7.3 to 15.4)	9.9 (4.0 to 15.1)	0.56
RV TDI velocity E′ (cm/s)	−12.5 (−6.9 to −19.3)	−11.5 (−7.1 to −19.4)	0.21
RV TDI velocity A′ (cm/s)	−8.4 (−2.7 to −14.2)	−7.6 (−1.6 to −19.1)	0.45

Table 6 Comparing patients with anthracyclines exposure in utero to those exposed to other chemotherapies

	Anthracyclines (49)	Nonanthracyclines (13)	*p* values
Age (years)	1 (1.8 to 9.8)	1.5 (1.4 to 9)	0.58
Male/female	30/19	6/7	0.39
BSA (m^2)	0.56 (0.42 to 1.38)	0.61 (0.42 to 1.00)	0.99
Heart rate (beats/min)	109 (57 to 147)	121 (69 to 152)	0.22
Systolic blood pressure (mmHg)	100 (82 to 125)	112 (95 to 131)	0.03
Diastolic blood pressure (mmHg)	60 (48 to 77)	65 (56 to 78)	0.24
LV shortening fraction (%)	35 (29 to 46)	35 (32 to 44)	0.67
LV ejection fraction (%)	66 (57 to 79)	65 (61 to 76)	0.81
LVEDD (cm)	3.10 (2.50 to 4.50)	3.00 (2.30 to 4.30)	0.33
LVEDD *z* score	0.22 (−2.00 to 3.19)	−0.13 (−2.36 to 1.42)	0.25
RVEDD (cm)	1.40 (0.93 to 2.20)	1.40 (1.00 to 1.70)	0.39
RVEDD *z* score	0.72 (−1.50 to 2.10)	0.44 (−1.08 to 1.30)	0.18
LVPW thickness	0.42 (0.29 to 0.7)	0.41 (0.31 to 0.51)	0.47
LVPW thickness *z* score	−0.07 (−2.32 to 1.81)	−0.22 (−1.83 to 1.81)	0.54
IVS thickness	0.40 (0.34 to 0.60)	0.40 (0.35 to 0.50)	0.30
IVS thickness *z* score	−0.96 (−2.50 to 1.30)	−1.06 (−2.62 to 0.16)	0.27
Mitral Doppler E/A ratio	1.7 (1.2 to 2.6)	1.5 (1.0 to 2.6)	0.51
IVRT (ms)	44 (32 to 81)	50 (32 to 57)	0.07
LV mean longitudinal strain (%)	20 (13 to 27)	19 (16 to 27)	0.13
LV mean circumferential strain (%)	20 (10 to 26)	19 (15 to 22)	0.33
LV TDI velocity S′ (cm/s)	5.3 (2.9 to 10.0)	5.8 (3.7 to 7.2)	0.73
LV TDI velocity E′ (cm/s)	−11.0 (−3.5 to −15.7)	−12.8 (−4.9 to −16.1)	0.54
LV TDI velocity A′ (cm/s)	−3.8 (−1.0 to −10.4)	−5.0 (−0.9 to −6.5)	0.38
IVS TDI velocity S′ (cm/s)	5.9 (4.8 to 8.4)	5.9 (4.3 to 7.1)	0.51
IVS TDI velocity E′ (cm/s)	−10.3 (−6.7 to −14.7)	−10.80 (−4.2 to −15.6)	0.15
IVS TDI velocity A′ (cm/s)	−4.6 (−0.7 to −10.2)	−5.5 (−0.6 to −7.4)	0.58
RV TDI velocity S′ (cm/s)	10.0 (7.3 to 15.4)	11.0 (9.1 to 14.3)	0.09
RV TDI velocity E′ (cm/s)	−12.5 (−6.9 to −19.3)	−13.9 (−11.7 to −22.4)	0.07
RV TDI velocity A′ (cm/s)	−8.4 (−2.7 to −14.2)	−9.39 (−6.5 to −14.7)	0.32

Discussion

This is a prospective cohort study looking at the effects of maternal malignancy and fetal exposure to chemotherapy on cardiac function after birth and during early childhood. In a previous report, we included a smaller cohort of patients and only used conventional echocardiographic measurements for assessing systolic function [9]. The current study includes 13 additional patients and also uses newer echocardiographic techniques for assessing myocardial function including tissue Doppler and myocardial deformation imaging. These techniques have been proven to be useful in detecting early dysfunction in anthracycline patients when ejection fraction is still preserved [10, 11, 13, 18]. We found that patients exposed to fetal chemotherapy had a statistically significant lower left ventricular wall thickness and ejection fraction when compared to the normal control group. Tissue Doppler velocities as well as global systolic strain measurements however were similar between the two groups.

Although ejection fraction and fractional shortening were significantly lower in the patient group, all EF and FS measurements were within normal range. It should be noted however that the values in the control group were in the higher range of reported normal control values, possibly influencing the interpretation of the results. In contrast to the previous study [9], we also found that LV wall thickness measurements were mildly reduced in the patient group compared to the normal control group. This difference was only noted to be present when the measurements were expressed as *z* scores but not when the absolute measurements were compared. *z* scoring corrects the dimensions for BSA and expresses them in standard deviations relative to mean measurements obtained in a normal population. We have no good explanation why the *z* scores for wall thickness would be different between the two groups while the absolute measurements were not statistically different. The BSA was similar for both groups. Our reference population on which the scores were based was a normal study group in Toronto which could potentially have induced

some bias in the *z* scores, although the average *z* scores for the normal control group were close to zero (−0.1 for IVS thickness and 0.5 for LVPW thickness). This suggests that the measurements in our study group and the Toronto reference group were very comparable. As anthracycline toxicity can result in loss of cardiac muscle, thinning of the LV walls has been previously shown as one of the first signs of the anthracycline toxicity [19]. This finding in patients after fetal exposure is possibly important as this might indicate that the fetal chemotherapy could be associated with myocardial cell loss. Interestingly, we found no significant difference between patients exposed to anthracyclines and patients treated with other chemotherapeutic agents. This also indicates that the current findings need to be interpreted cautiously. Further study is required in larger patient group and further prospective follow-up of the current group will hopefully be able to answer the clinical relevance of the small changes we observe.

Tissue Doppler and strain imaging have been demonstrated to be able to identify early changes in myocardial function prior to changes in overall cardiac function. Especially in patients exposed to anthracyclines this has been shown to precede changes in ejection fraction and fractional shortening [10, 11, 13, 18]. The observation that no significant differences in tissue Doppler and strain imaging can be detected between the patients and the normal controls is therefore reassuring and suggests that there are no significant changes in myocardial function that can be detected at young age. This also seems to suggest that the small difference observed in ejection fraction is probably not really clinically important as it is not accompanied by any other changes in functional parameters.

The use of chemotherapy and especially anthracyclines during pregnancy does not seem be associated with a high risk for cardiotoxicity after birth. Recent data have suggested that there is limited transplacental materno-fetal transfer of chemotherapeutic agents in a baboon model [20–22] but no good human data are available. Our data are supported by Aviles et al. who demonstrated normal ejection fractions in older children and adults after maternal chemotherapy [23]. Further prospective data are required and careful follow-up of this patient cohort is required.

Limitations

This is a multicenter study with data acquisition at three different sites. This introduces some variability. We tried to avoid this by well standardizing the imaging protocols and by having the data analyzed in a central core lab by a single observer. We previously tested the interobserver variability for tissue Doppler and strain measurements in the core lab and data have been published [16, 17, 24]. To minimize the influence of poorly recorded data especially in the non-sedated patients, we excluded studies that did not meet quality criteria. The *z* scores used are based on a normal control group from Toronto, which is ethnically different from the study group. This may have influenced some of the *z* scoring results. To compensate for the high diversity in Toronto we have added additional normal controls from the Belgian group. Another limitation is that we cannot exclude a potential effect of a higher incidence of preterm delivery in the fetal exposure group. In total 66 % of the chemotherapy patients were born preterm and this could have a potential effect on cardiac growth parameters and cardiac dimensions. A study performed on the outcome of fetuses with intrauterine growth retardation has shown that the LV can remodel differently and we cannot exclude a similar effect in our study population [25]. Ideally, the control group should include a similar number of preterm infants not exposed to intrauterine chemotherapy to correct for this potential effect. This is however a very difficult study to perform as there will be many confounding factors in the preterm group. The patient cohort is still relatively small and still might lack sufficient power to detect smaller differences in cardiac dimensions and functional parameters, given the intrinsic variability of echocardiographic measurements. We hope to overcome this limitation by further recruitment and provide further prospective follow-up data on this cohort in the future. We therefore continue this study within a European framework (www.cancerinpregnancy.org).

Conclusion

This study indicates that young children exposed to prenatal chemotherapy might have minor changes in LV wall thickness associated with a slightly lower but normal ejection fraction. Myocardial function as assessed by tissue Doppler velocities and strain imaging is normal and not different between patients and controls. Based on our data, maternal chemotherapy does not seem to result in cardiomyopathy or cardiac dysfunction during early childhood. Further long-term follow-up data are however required to rule out an effect later on in life.

Acknowledgments Frederic Amant is senior clinical researcher for the Research Foundation-Flanders (F.W.O.) This research is supported by Research Foundation-Flanders (F.W.O.) Project G. 0358.06, 'Stichting tegen kanker Project SCIE2006-17', Research Fund-K.U.Leuven (OT/07/053), Clinical Research Fund-UZ Gasthuisberg, and Belgian Cancer Plan, Ministry of Health NKP 29 038.

Conflict of interest None declared.

References

1. Amant F, Han SN, Gziri MM, Dekrem J, Van Calsteren K (2012) Chemotherapy during pregnancy. Curr Opin Oncol 24(5):580–586. doi:10.1097/CCO.0b013e328354e754

2. Amant F, Van Calsteren K, Halaska MJ, Gziri MM, Hui W, Lagae L, Willemsen MA, Kapusta L, Van Calster B, Wouters H, Heyns L, Han SN, Tomek V, Mertens L, Ottevanger PB (2012) Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. Lancet Oncol. doi:10.1016/S1470-2045(11)70363-1
3. Aviles A, Neri N, Nambo MJ (2006) Long-term evaluation of cardiac function in children who received anthracyclines during pregnancy. Ann Oncol 17(2):286–288. doi:10.1093/annonc/mdj053
4. Calsteren KV, Verbesselt R, Devlieger R, De Catte L, Chai DC, Van Bree R, Heyns L, Beijnen J, Demarsin S, de Bruijn E, de Hoon J, Amant F (2010) Transplacental transfer of paclitaxel, docetaxel, carboplatin, and trastuzumab in a baboon model. Int J Gynecol Cancer 20(9):1456–1464. doi:10.1111/IGC.0b013e3181fb18c8
5. Cardonick E, Dougherty R, Grana G, Gilmandyar D, Ghaffar S, Usmani A (2010) Breast cancer during pregnancy: maternal and fetal outcomes. Cancer J 16(1):76–82. doi:10.1097/PPO.0b013e3181ce46f9
6. Cardonick E, Usmani A, Ghaffar S (2010) Perinatal outcomes of a pregnancy complicated by cancer, including neonatal follow-up after in utero exposure to chemotherapy: results of an international registry. Am J Clin Oncol 33(3):221–228. doi:10.1097/COC.0b013e3181a44ca9
7. Crispi F, Bijnens B, Figueras F, Bartrons J, Eixarch E, Le Noble F, Ahmed A, Gratacos E (2010) Fetal growth restriction results in remodeled and less efficient hearts in children. Circulation 121 (22):2427–2436. doi:10.1161/CIRCULATIONAHA.110.937995
8. Fallah-Rad N, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, Tian G, Kirkpatrick ID, Singal PK, Krahn M, Grenier D, Jassal DS (2011) 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(22):2263–2270. doi:10.1016/j.jacc.2010.11.063
9. Friedberg MK, Mertens L (2009) Tissue velocities, strain, and strain rate for echocardiographic assessment of ventricular function in congenital heart disease. Eur J Echocardiogr 10(5):585–593. doi:10.1093/ejechocard/jep045
10. Friedberg MK, Mertens L (2012) Deformation imaging in selected congenital heart disease: is it evolving to clinical use? J Am Soc Echocardiogr 25(9):919–931. doi:10.1016/j.echo.2012.06.008
11. Ganame J, Claus P, Eyskens B, Uyttebroeck A, Renard M, D'Hooge J, Gewillig M, Bijnens B, Sutherland GR, Mertens L (2007) Acute cardiac functional and morphological changes after Anthracycline infusions in children. Am J Cardiol 99:974–977
12. Ganame J, Claus P, Uyttebroeck A, Renard M, D'Hooge J, Bijnens B, Sutherland GR, Eyskens B, Mertens L (2007) Myocardial dysfunction late after low-dose anthracycline treatment in asymptomatic pediatric patients. J Am Soc Echocardiogr 20(12):1351–1358. doi:10.1016/j.echo.2007.04.007
13. Gziri MM, Debieve F, DEC L, Mertens L, Barrea C, VANC K, Han SN, Heyns L, Amant F (2012) Chemotherapy during pregnancy: effect of anthracyclines on fetal and maternal cardiac function. Acta Obstet Gynecol Scand. doi:10.1111/j.1600-0412.2012.01524.x
14. Koopman LP, Slorach C, Hui W, Manlhiot C, McCrindle BW, Friedberg MK, Jaeggi ET, Mertens L (2010) Comparison between different speckle tracking and color tissue Doppler techniques to measure global and regional myocardial deformation in children. J Am Soc Echocardiogr 23(9):919–928. doi:10.1016/j.echo.2010.06.014
15. Koopman LP, Slorach C, Manlhiot C, McCrindle BW, Friedberg MK, Mertens L, Jaeggi ET (2010) Myocardial tissue Doppler velocity imaging in children: comparative study between two ultrasound systems. J Am Soc Echocardiogr 23(9):929–937. doi:10.1016/j.echo.2010.06.028
16. Koopman LP, Slorach C, Manlhiot C, McCrindle BW, Jaeggi ET, Mertens L, Friedberg MK (2011) Assessment of myocardial deformation in children using digital imaging and communications in medicine (DICOM) data and vendor independent speckle tracking software. J Am Soc Echocardiogr 24(1):37–44. doi:10.1016/j.echo.2010.09.018
17. Lipshultz SE, Lipsitz SR, Sallan SE, Dalton VM, Mone SM, Gelber RD, Colan SD (2005) Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. J Clin Oncol 23(12):2629–2636
18. Reynoso EE, Huerta F (1994) Acute leukemia and pregnancy-fatal fetal outcome after exposure to idarubicin during the second trimester. Acta Oncol 33(6):709–710
19. Reynoso EE, Shepherd FA, Messner HA, Farquharson HA, Garvey MB, Baker MA (1987) Acute leukemia during pregnancy: the Toronto Leukemia Study Group experience with long-term follow-up of children exposed in utero to chemotherapeutic agents. J Clin Oncol 5 (7):1098–1106
20. Sawaya H, Plana JC, Scherrer-Crosbie M (2011) Newest echocardiographic techniques for the detection of cardiotoxicity and heart failure during chemotherapy. Heart Fail Clin 7(3):313–321. doi:10.1016/j.hfc.2011.03.003
21. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, Gosavi S, Carver JR, Wiegers SE, Martin RP, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M (2011) Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol 107(9):1375–1380. doi:10.1016/j.amjcard.2011.01.006
22. Scully RE, Lipshultz SE (2007) Anthracycline cardiotoxicity in long-term survivors of childhood cancer. Cardiovasc Toxicol 7 (2):122–128
23. Van Calsteren K, Verbesselt R, Beijnen J, Devlieger R, De Catte L, Chai DC, Van Bree R, Heyns L, de Hoon J, Amant F (2010) Transplacental transfer of anthracyclines, vinblastine, and 4-hydroxy-cyclophosphamide in a baboon model. Gynecol Oncol 119(3):594–600. doi:10.1016/j.ygyno.2010.08.019
24. Van Calsteren K, Verbesselt R, Van Bree R, Heyns L, de Bruijn E, de Hoon J, Amant F (2011) Substantial variation in transplacental transfer of chemotherapeutic agents in a mouse model. Reprod Sci 18(1):57–63. doi:10.1177/1933719110379650
25. Yeh ET, Bickford CL (2009) Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol 53(24):2231–2247. doi:10.1016/j.jacc.2009.02.050