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Mohamed Jaber

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UNIVERSITÉ CLERMONT AUVERGNE  
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

pour le

DIPLOME D'ÉTAT DE DOCTEUR EN MÉDECINE

par

JABER Mohamed

Présentée et soutenue publiquement le 07/04/2023

**ANTHRACYCLINE-INDUCED CARDIOTOXICITY ON REGIONAL  
MYOCARDIAL WORK AND LEFT VENTRICULAR MECHANICAL DISPERSION  
IN YOUNG ADULTS IN POST-LYMPHOMA REMISSION**

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*Vous nous faites l'honneur d'accepter la présidence de notre jury de thèse*

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Cardiologie

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## **ABBREVIATIONS**

**AFI** : Automatic Function Imaging

**AIC**: anthracycline induced cardiotoxicity

**ANOVA** : One-way analysis of variance

**BMI** : body mass index

**BP** : Blood pressure

**CLS** : childhood lymphoma survivors

**ECG** : Electrocardiogram

**GLS** : Global Longitudinal Strain

**LVD** : Left ventricular dyssynchrony

**LVEF** : left ventricular ejection fraction

**MCW** : myocardial constructive work

**MW** : Myocardial work

**MWE**: myocardial work efficiency

**MWI** : myocardial work index

**MWW** : myocardial wasted work

**PSL** : pressure-strain loops

**SD** : standard deviation

**STE** : speckle tracking echocardiography

**TTP** : time to peak

## **Abstract**

**Background:** The cardiac-induced toxicity of chemotherapy including anthracycline is well-described in childhood lymphoma survivors (CLS).

**Objective:** Myocardial work (MW) is a new echocardiographic tool with a high sensibility to detect early and subtle alterations of myocardial function. We aimed to evaluate the late effects of anthracycline by assessing the global and segmental MW and intraventricular mechanical dispersion from speckle tracking echocardiography in CLS.

**Methods:** Thirty-one young adults including 16 CLS and 15 age-matched healthy controls were enrolled in the study. All underwent a resting echocardiography including an evaluation of left ventricular (LV) morphology and regional myocardial function. We assessed LV longitudinal (differentiating sub-endocardial and sub-epicardial layers), circumferential strains and twist, LV myocardial regional strains and MW. LV mechanical dispersion was assessed from the time dispersion of LV longitudinal strain and from myocardial wasted work (MWW) and myocardial work efficiency (MWE).

**Results:** The longitudinal strains both at the level of the sub-endocardium and sub-epicardium was reduced in CLS compared to controls. The global MW index (MWI) was also decreased ( $1668 \pm 266$  vs  $1870 \pm 264$  %. $\text{mmHg}$  in CLS patients and controls, respectively,  $P < 0.05$ ), especially on the apical segments. An increase of LV intraventricular mechanical dispersion was observed in CLS. However, MWW and MWE remained unchanged compared to controls.

**Conclusion:** Our results strongly support that cardiac remodeling is observed in CLS, characterized by a decrease in longitudinal strains and MW and an increase in LV mechanical dispersion. Specific alteration of the apex is present, but its causes and its clinical significance remain to be explored.

## 1. INTRODUCTION

Childhood cancer is a heterogeneous group of malignancies. Among adolescents, the most common cancer groups are lymphoma (27%). Five-year cancer survival exceeds 80 % in most European and North American countries today [1,2], especially with chemotherapy, which usually combines antineoplastic drugs whose anthracyclines. The aim of current international protocols is to reduce intensity of chemotherapy without threatening survival, in order to limit its toxicity, particularly on the cardiovascular system. Indeed, cardiovascular complications are one of the leading causes of morbidity and mortality among childhood cancer survivors, especially with anthracyclines which have an almost six-fold increased risk for heart failure compared to their siblings, with an increasing incidence with prolonged survival [3–5]. The appearance of chemotherapeutic cardiotoxicity may indicate the interruption of treatment [6,7], and therefore cardiotoxicity is an important prognostic factor.

Clinical guidelines of cardiology and oncology societies on prevention and treatment of anthracycline-induced cardiotoxicity (AIC) focused on screening for left ventricular ejection fraction (LVEF) reduction throughout the treatment [8,9]. Recently, the American Society of Echocardiography and European societies recommended the Global Longitudinal Strain (GLS), from speckle tracking echocardiography (STE), as a marker of myocardial dysfunction [8–11]. Indeed, it may provide an early warning sign of evolving cardiomyopathy among childhood-cancer survivors treated with anthracyclines despite their normal LVEF [12–15]. However, GLS represents only one component of LV strains. A comprehensive approach to assess LV systolic function needs to combine GLS with circumferential strains [16], and also LV twisting mechanics [17]. During systole, due to the complex orientation of the myocardial fibers, LV twists consequently to the opposing rotations of the base and the apex, which is essential to maintain efficiency of systolic function. Significant reduction of twist and untwist velocities

were observed in childhood lymphoma survivors (CLS) [17,18]. Another important feature is to propose a regional assessment of LV strain [16] and a differentiation of subendocardial and subepicardial layers that could provide additional information on the subtle myocardial remodeling in CLS.

Recently, Myocardial work (MW), obtained by integrating both cardiac deformation and non-invasive LV pressure has been proposed as an additional echocardiographic tool to detect subtle LV dysfunctions [19,20]. In adults population, MW has already been evaluated in many diseases and previous work demonstrated its better sensitivity in predicting coronary artery disease and assess early subclinical ischemic myocardial dysfunction compared to GLS [21]. Importantly, MW can be assessed regionally, according to a 18-segments model of the LV. However, its global and regional assessment in CLS remains to be evaluated.

Myocardial performance can also be altered by the non-uniform contractions of LV myocardial walls, that could led to a LV dyssynchrony (LVD) characterized by an increased mechanical timing dispersion at end systole. In childhood cancer survivors, previous studies showed structural myocardial abnormalities with presence of diffuse interstitial fibrosis, and sarcomeric disruption [5,22]. Since interactions exist between myocardial fibrosis and conduction disorders [23], we questioned a potential increase of LV mechanical dispersion in CLS. The LV mechanical dispersion, never explored in this specific population, can be assessed not only from the segmental analysis of timing of LV strains, but also from the MW. Indeed, a study of MW, which includes myocardial constructive (MCW) and wasted work (MWW), could reveal an increase in mechanical dispersion via an increase in MWW [24].

In this context, the objective of the study was to compare the cardiac function of CLS, with healthy age-matched controls, to determine the late effects of anthracyclines by assessing not only myocardial strain, but also MW and LV mechanical dispersion. We hypothesized that CLS

treated with anthracyclines have adverse cardiac remodeling characterized by 1) a decrease of longitudinal strain, especially in the subendocardial layer, 2) a decrease of segmental and global MW, 3) increase of LV intraventricular mechanical dispersion associated with an increase of MWW.

## **2. MATERIALS AND METHODS**

### **2.1 Study design and population**

This study collected the data of our previous prospective cross-sectional case-control study run from January 2022 to May 2022 in Clermont-Ferrand University Hospital, France. 16 CLS were included and compared with 15 healthy controls, recruited from the database of the Centre d'Investigation Clinique of Clermont-Ferrand University Hospital, and matched for sex, age ( $\pm 5$  years), and body mass index ( $\text{BMI} \pm 5 \text{ kg/m}^2$ ). None of the participants had cardiac medication at the time of evaluation and all were normotensive and in sinus rhythm. CLS aged between 18-25 years old were followed for childhood lymphoma post-therapeutic surveillance, and considered as recovered (i.e., free of any lymphoma medication or radiotherapy for at least one year), with no physical disability at the day of inclusion. To guarantee a late cardiac functional assessment and the absence of any progressive malignancy, only patients who have recovered of treatment for over 2 year, up to 10 years, were eligible for the study. Subjects were excluded if they had been clinically diagnosed for a running infection or undergone corticosteroid treatment within the last three months before the day of visit. Approval was granted by the Comité de Protection des Personnes Sud-Est V (no. 21.02921.000036 cat 1). Written informed consents were collected from every participant on the day of visit in line with the principles of the Declaration of Helsinki.

### **2.2 Anthropometrics**

Height was determined using a mural stadiometer with subject barefoot (graduated in cm, precision of 0.5 cm), and weight using a digital weight scale (graduated in kg, with 0.1 kg precision), permitting calculation of BMI ( $\text{body weight} \cdot \text{body height}^{-2}$ , with weight in kg and height in m). Blood pressure (BP) were recorded at rest, using an automatic device (General Electric Dynamap PRO 300 V2, Boston, MA, USA).

### **2.3 Biological data**

Blood samples were collected after 12 hours fasting and at least 10 minutes resting. The two main cardiotoxicity biomarkers, troponin I and N-Terminal pro-brain natriuretic peptide (NT-proBNP), were assessed in all participants. Standard blood test as haemoglobin, C-reactive protein, thyroid hormones and albumin were also performed to identify biological anomalies, which could influence cardiac parameters.

### **2.4 Echographic conventional recordings**

Echocardiography was carried out with the subject in the left lateral decubitus position, with Vivid ultrasound systems (GE Healthcare, Horten, Norway) using a 3.5 MHz transducer (M4S probe), by the same, experimented, cardiologist, blinded of the status of patients. 2D echocardiographic measurements were made in accordance with the American Society of Echocardiography guidelines [25]. Cine loops are stored in one R–R interval length to facilitate easy analysis. Electrocardiogram (ECG) signal is recorded for R–R interval clip storage and no ambiguous ECG complexes or leading T-waves were displayed. Interventricular septum thicknesses were measured from the parasternal long axis view. LV volumes and LVEF were assessed using the Simpsons biplane method. Stroke volume and cardiac output were assessed from a 5-chamber view and then indexed to body surface area. LV mass was estimated by the Lang formula and indexed to body surface area. Diastolic function was assessed by doppler from peak early (E) and atrial (A) trans-mitral flow velocities. Septal and lateral E' wave from tissue doppler completes this evaluation. The LV filling pressures were evaluated from the E/E' ratio.



## 2.5 Two-dimensional strain analysis from STE

Cine loops were recorded in parasternal long and short axis (basal and apical) and apical (5, 4, 2, and 3 chambers) views and saved for blinded off-line analysis (EchoPAC, BT204 Version, GE Healthcare), with ECG recording. Data was normalized to percentage of systolic duration to avoid differences in heart rate and cine loops frame rates. We used an 18-segments model from apical 4-, 2-, and 3-chambers views to assess LV regional strains and time to peak (TTP) strains in accordance with the nomenclature of Lang et al [25]. A segment-by-segment validation must be done to continue the analysis. When analysis was not possible or unreliable, the segment or cut was excluded from the analysis. Systolic and diastolic strain rates were then obtained from time-derivation of strains. The diastolic longitudinal strain rate (diastolic GLS-rate) was used as an indicator of LV relaxation [26].

LV twisting mechanics were assessed by STE using two-dimensional images from the apical and basal short-axis planes previously stored. Basal planes were assessed regarding the mitral valve and apical planes toward the apex with no visible papillary muscles. With LV contraction, the cardiac apex and the base rotates in counterclockwise and clockwise directions, respectively, when viewed from the apex. Twist represents the mathematical difference in the rotation of the apex and base, at each percentage of systolic duration [27]. Peak systolic twisting velocity was defined by the peak positive rate of torsional deformation, whereas the peak diastolic untwisting velocity was defined by the peak negative rate of torsional deformation. Untwisting velocity is thought to be an important initial manifestation of active relaxation.

The LV mechanical dispersion was quantified by calculating the standard deviation (SD) of the TTP systolic strain in the longitudinal direction in the 18-segments model ( $SD_{18S}$ ), and the maximum delay between the segments with earliest and the latest TTP ( $\Delta 1-18$ ).

## 2.6 Myocardial work

MW was estimated using the Automatic Function Imaging (AFI) of the Echo PAC software (Version 203; GE Healthcare). MW was assessed as a function of time throughout the cardiac cycle by the combination of LV strain data (recorded on the apical 4-, 3-, and 2-chambers views) obtained by STE and a non-invasively estimated LV pressure curve as previously described [28]. The result was integrated over time to obtain MW as a function of time. MW was calculated from mitral valve closure until mitral valve opening as previously described. The valvular markers of mitral and aortic opening and closure were taken first on the doppler from peak early (E) and atrial (A) trans-mitral flow and trans-aortic, for reproducibility, and then imported into the MW analysis with a secondary modification on the 2D section for synchronization. All data are averaged on 2 cardiac cycles, synchronized with ECG, and we assumed that high and low pressure measured was equal to peak systolic and diastolic LV pressures and to be uniform throughout the ventricle. Strain and MW evaluation was done by a single investigator. The global or segmental myocardial work efficiency (MWE) depends on the MCW and MWW, and was obtained as follows:

$$MWE = \frac{MCW}{MCW + MWW} \times 100$$

In systole, the work performed by the myocardium during segmental shortening represents MCW (includes lengthening in isovolumic relaxation), whereas the work performed by the myocardium during stretch or segmental lengthening represents the energy loss, which is defined as MWW. For both global and segmental analyses, we constructed LV pressure-strains loops. The area of the loops represented the Myocardial work index (MWI).

## **2.7 Statistical analysis**

All values were expressed as mean  $\pm$  SD. Statistical analyses were performed using Medcalc (version 19.1, Medcalc Software). One-way analysis of variance (ANOVA) was used to compare groups, after checking the normality of distribution of each variable by the Shapiro-Wilk test. In the absence of normal distribution, the nonparametric Kruskal-Wallis test was used. Statistical significance for all analyses was assumed at  $p < 0.05$ .

### **3. RESULTS**

#### **3.1 Participants characteristics**

Clinical data of the two populations are presented in [Table 1](#). The median time interval between the end of chemotherapy and patient enrolment was 7 years. CLS were treated by chemotherapy with a mean cumulative dose of anthracyclines of 160 mg.m<sup>-2</sup> with a maximal dose of 286 mg.m<sup>-2</sup> in one patient. Doxorubicine was mainly used. Mean corticosteroids was 2600 mg.m<sup>-2</sup>. Alkylant-agent and type II topo-isomerase inhibitor were used for all patients. Four Hodgkin lymphoma survivors had a total of 19.6 Gy mediastinal and cervical targeted radiation therapy (depending on diagnosis stage or relapse) and 2 benefited of autologous hematopoietic stem cell transplantation for relapse.

There was no significant difference between CLS and healthy controls in term of blood pressure. No patient had symptoms of heart failure. Heart rate was significantly higher in CLS compared to controls. No statistical difference was shown on troponin I and NT-proBNP, with a mean value of 51 ± 33 ng.L<sup>-1</sup> in CLS. Haemoglobin was higher in CLS. None participant had anemia. Non-significative difference was found on CRP, negative for all, thyroid hormone nor on nutritional status estimated by albumin levels .

#### **3.2 Left ventricular morphology and function**

Data of LV morphology and function are presented in [Table 2](#). LV posterior wall thickness, LV septum thickness, LV end-diastolic and end-systolic volume, LV mass and LV mass indexed to body surface area were comparable in both population. LVEF was significantly decreased in CLS patients but no LVEF below 60% was detected. There was no significant difference in the early to late diastolic filling ratio (E/A ratio) and E/E' ratio.

### **3.4 Left ventricular regional strains and myocardial work**

LV strains are presented in [Table 3](#) and [Figure 1](#). GLS was diminished in CLS patients compared to controls, whereas no difference was observed on circumferential strains. We note a significant and similar difference in both sub-endocardium and sub-epicardium in CLS compared to controls. In CLS, the global strain rate values were significantly inferior and we note significant difference in Diastolic GLS-rate. LV twisting mechanics are presented in [Table 3](#) and [Figure 2](#). LV rotations and twist were similar between groups despite their patterns during the cardiac cycle appears slightly different. Peak untwisting rate, which occurred in very early diastole, was lower in CLS compared to controls.

MW data are presented in [Table 4](#) and [Figure 3](#). In CLS patients, the LV pressure-strain loops (PSL) was shifted to the right, consequently to the decrease of their GLS. The MWI, calculated as the area of the PSL, was significantly different between groups ( $1668 \pm 266$  vs  $1870 \pm 264$  % .mmHg in CLS patients and controls, respectively). In CLS, segmental MWI values presented in [Figure 4](#) were significantly lower in the apical segments, whereas no significant difference was showed in the mid and basal segments.

### **3.5 Left ventricular mechanical dispersion**

The  $SD_{185}$  and the Delta1-18, markers of intraventricular mechanical dispersion, were significantly increased in the CLS group ([Table 4](#)). No difference was however observed between groups regarding the MWW, and consequently the MWE was unchanged.

#### 4. DISCUSSION

The aim of our study was to compare the cardiac function of CLS with age-matched control subjects to determine the late anthracyclines cardiotoxicity using STE. In CLS, we observed 1) a reduction of longitudinal strains in a similar manner in the sub-endocardium and sub-epicardium, without alteration of circumferential strains and twist 2) a decrease of MW, mainly observed on segmental analysis with specific alteration in apex, 3) an increase of LV intraventricular mechanical dispersion, but without significant alteration of MWW and global MWE.

##### *Lower longitudinal strain without alteration of circumferential strains and twist in CLS*

The first result of our study was that GLS, which allows a more sensitive analysis of systolic function than LVEF, was significantly lower in CLS than in controls although they received relatively low doses of anthracyclines. Of note, whereas GLS was decreased, LV CS, rotations and twist were unchanged in CLS. The LV twist plays an important role to promote LV ejection during systole, therefore the maintenance of LV twist in CLS probably contributed to maintain their LVEF despite the decrease of the GLS. Similar pattern of impaired GLS without changes in CS was documented in young patients after chemotherapy [13,16,18,29], but also in patients suffering of hypertrophic cardiomyopathy [30]. Since sub-endocardial layer is principally composed of fibers oriented longitudinally, it has been often hypothesized that sub-endocardial layer was more sensitive to myocardial disease such as fibrosis. For example, lower CS is found in transmural myocardial infarction, differentiating it from subendocardial infarction [13]. In adults with an AIC [23,31] previous studies observed that the late gadolinium cardiac magnetic resonance was enhanced specifically in the sub-endocardium, suggesting the presence of fibrosis. However, our results indicated that the decrease of LS was similar on both layers, that

spoke in favor of an homogeneous alteration of the different zones of the myocardium rather than a specific alteration of the sub-endocardial layer.

During systole, contraction of the cardiomyocytes generates opposite rotations of the LV base and apex, inducing a LV twist. This mechanism predominantly deforms the subendocardial fiber matrix, resulting in storage of potential energy. Subsequent untwist deformation is associated with the release of restoring forces, which contributes to LV diastolic relaxation and early filling which onset and peak could be significantly delayed in diastolic heart failure [32]. In our study, we observed that untwisting rate was lowered in CLS despite their normal LV twist. This result has been described by others [17,33] and support that underlying mechanisms of diastolic function were altered in CLS patients with a potential decrease of LV intrinsic myocardial relaxation.

#### *Specific decrease of apical MW in CLS*

Non-invasive PSL as a surrogate of MW have been validated by many studies and distinguished itself by an overcome of EF and LS load dependency [34–37]. Indeed, MW takes into account deformation as well as afterload through interpretation of strain in relation to dynamic non-invasive LV pressure (estimated by measurement of cuff pressures). This estimation of MW was already studied in preclinical and adults cohorts of patients [19,20,38]. For example, MW has been assessed in ischemic cardiac disease, allowing to detect subclinical coronary artery disease without any regional wall motion abnormalities, and had more important sensitivity for myocardial oxygen consumption [21]. In pediatric population, Zhan et al. recently demonstrated that global MWI enhanced hypertensive heart disease evaluation and cardiac dysfunction during and after chemotherapy follow-up [37,39]. In our study, while systolic BP were similar between the two groups, the MWI was reduced in CLS, linked in a large part to their lower GLS.

The strength of our study was to assess not only global MW, but also segmental MW. Based on regional assessments on a 18-segments model of the LV, we observed that MW was specifically decreased in the apical region. To our knowledge, no previous studies assessed the segmental MWI in CLS. This result was in agreement with previous study, showing impaired LS specifically in apical segments, in a cohort of childhood-cancer survivors [16,40–42]. We also noticed a specific and significant decrease of MW on the basal inferior in CLS compared to controls, whereas other basal segments remained strictly unchanged. The clinical significance and the underlying mechanisms of this regional alteration remains unclear. Specific segmental modifications of MW have already been showed in adult populations for precising diagnosis, or as a predictor of mortality by evaluation of its apex-to-base ratio in cardiac amyloidosis, or as short-term prognosis markers in ischemic diseases or post-therapeutic prediction response in cardiac resynchronization therapy [34]. In our population and on the basis of preclinical *in-vivo* juvenile rat's study, our result can suggest starting fibrosis pattern in the apical regions in CLS [43]. Apical deterioration might be also explained by the extent of sensitivity toward the LV apical vortex, which is formed by the helical fibers that exist without any surrounding circumferential muscle [13]. Further investigations are needed to explore the role of the apex in myocardial mechanics and its specific implication in long-term cardiac dysfunction in CCS.

#### *Higher intraventricular mechanical dispersion in CLS*

Interstitial fibrosis was detected in microscopic slides of heart tissue from patients who had cardiac transplants after AIC, without significant cardiac hypertrophy [44]. Myocardial fibrosis having adverse effects on excitability, sarcomeric organization, and the regulation of intracellular calcium and myofilament Ca<sup>2+</sup> sensitivity [43,45], these myocardial alterations could increase mechanical dispersion and decrease myocardial efficiency. Based on segmental



STE analysis, we observed that SD18S and delta 1-18, both overall indexes of LV mechanical dispersion, were significantly increased in CLS compared to controls. Others studies also showed increased systolic intraventricular dyssynchrony index in childhood-cancer survivors, with significant negative correlations with LVEF [46,47]. To complete the study of mechanical dispersion, we measured MCW and MWW to calculate MWE. In patients with increased mechanical dispersion, MWW is generally increased and consequently MWE reduced. However, we did not significant alteration of both MWW and MWE in CLS compared to controls. These findings were nevertheless concordant with Zhan et al. showing preserved MWE [37].

#### *Study limitations*

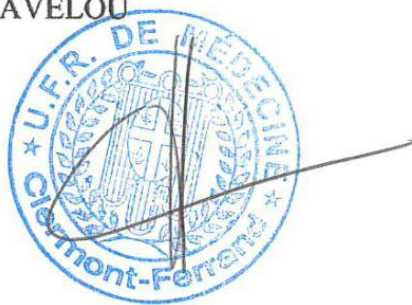
Our study has several limitations. First, this is a single center study including a small group of patients. However, despite the small sample size, our data clearly showed a significant impact of anthracycline on LV regional myocardial function assessed by 2D-strain echocardiography and MW. Moreover, we assessed only the late effects of anthracycline, several years after completion of therapy in CLS, and it would be interesting to have assess also the alteration of their cardiac function during the treatment. However, long-term effects of anthracyclines are known to develop even years after completion of treatment. Finally, it would be helpful to link the increase of the LV mechanical dispersion observed in CLS with a potential increase of myocardial fibrosis from magnetic resonance imaging with late gadolinium enhancement.

## 5. Conclusion

With more CLS now reaching adulthood, understanding the adverse effects of chemotherapy and particularly anthracyclines on the cardiovascular system is of major interest. Our results highlighted that the late cardiac effects of chemotherapy based on low to moderate doses of anthracyclines were characterized by a decrease of the GLS. The strength of our study was to assess the MW, a new echocardiographic tools which has been shown to be useful to detect early and subtle dysfunction in various pathologies. We observed that global MW was depressed in CLS. Based on a regional analysis, our data strongly supported that MW was diminished specifically on apical segments. Moreover, our regional analysis enabled an assessment of the intraventricular mechanical dispersion, which was higher in CLS compared to controls. All-in-one, our study strongly supported a late but subtle effect of chemotherapy based on anthracyclines in young adults. However, further studies would be helpful to evaluate the clinical significance of these cardiac remodeling and their potential long-term adverse cardiac events, in order to propose an adapted follow-up to CLS and evaluate the benefit of cardio-protective preventive therapies.

Le Doyen de l'UFR de Médecine

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## Annexes

**Table 1.** Baseline Characteristics of Patients and Controls

	<b>Patients (n = 16)</b>	<b>Controls (n=15)</b>
Age	21 ± 2	23 ± 1,5*
Male (n)	9 (56%)	7 (47%)
Female (n)	7 (44%)	8 (53%)
BMI	23,5 ± 3,2	22,3 ± 2,5
Heart rate at rest (bpm)	81 ± 13	70 ± 13*
Systolic BP (mmHg)	118	119
Diastolic BP (mmHg)	76,6 ± 9,6	74,9 ± 8,8
Mean BP (mmHg)	89,5 ± 10,3	88,0 ± 7,8
Hodgkin disease	12	
Non-Hodgkin lymphomas #	4	
Age at diagnosis (years)	14,7	
Cumulative dose of Anthracyclines (mg.m <sup>-2</sup> )	160 ± 37,4	
Time since end of treatment (years)	6,3 ± 2,4	
Radiotherapy (n)	4	
Haematopoietic stem cells transplantation for relapse (n)	2	
Other chemotherapy	All	

*Quantitative variables are expressed as mean ± standard deviation.*

*\*: significantly different from Controls (\*: p<0.05)*

*# Non Hodgkin lymphomas gather, one B and one T lymphoblastic lymphoma, one Grey zone lymphoma and one large B cells lymphoma.*

**Table 2.** Left ventricular morphology and function

	<b>Patients</b> (n = 16)	<b>Controls</b> (n=15)
<b>LV Morphology</b>		
LV septum thickness (cm)	0.84 ± 0.12	0.85 ± 0.17
LV posterior wall thickness (cm)	0.85 ± 0.16	0.91 ± 0.11
LV end-diastolic volume (mL)	114 ± 32	106 ± 27
LV end-systolic volume (mL)	33 ± 9	32 ± 8
LV mass (g)	145 ± 48	143 ± 38
LV mass/BSA	80 ± 11.5	83 ± 9.7
<b>LV systolic function</b>		
Ejection fraction (%)	65.2 ± 5.3 *	69.6 ± 6.3
<b>LV diastolic function</b>		
E wave (m.s <sup>-1</sup> )	0.86 ± 0.14	0.89 ± 0.15
A wave (m.s <sup>-1</sup> )	0.51 ± 0.08	0.57 ± 0.13
E/A	1.72 ± 0.33	1.59 ± 0.29
E/E' lat	4.5 ± 0.7	4.5 ± 0.9

*Values are mean ± SD*

*\*: significantly different from Controls (\*: p<0.05)*

*LV: left ventricular; BSA: body surface area*

**Table 3.** Left ventricular strains

	Patients (n = 16)	Controls (n=15)
<b>LV longitudinal strains</b>		
GLS (%)		
Myocardium	-14.2 ± 2.5 ***	-17.1 ± 1.6
Sub-endocardium layer	-16.6 ± 2.7 ***	-19.8 ± 2.4
Sub-epicardium layer	-11.5 ± 2.6 **	-14.1 ± 1.9
Systolic GLS-rate (.s <sup>-1</sup> )	-0.75 ± 0.11 **	-0.86 ± 0.06
Diastolic GLS-rate (.s <sup>-1</sup> )	1.26 ± 0.33 **	1.54 ± 0.24
<b>LV circumferential strains</b>		
CS (%)		
Basal level	-11.3 ± 1.4	-11.8 ± 3.8
Apical level	-19.4 ± 6.4	-19.3 ± 5.6
Systolic CS-rate (.s <sup>-1</sup> )		
Basal level	-0.79 ± 0.11	-0.82 ± 0.23
Apical level	-1.22 ± 0.45	-1.23 ± 0.29
Diastolic CS-rate (.s <sup>-1</sup> )		
Basal level	1.15 ± 0.31	1.32 ± 0.42
Apical level	1.62 ± 0.39	1.82 ± 0.63
<b>LV Twisting mechanics</b>		
Rotations (deg)		
Basal level	-4.5 ± 2.6	-3.6 ± 1.9
Apical level	6.1 ± 2.6	6.6 ± 2.3
Twist (deg)		
	7.7 ± 3.2	8.1 ± 3.7
Untwisting rate (°·s <sup>-1</sup> )		
	- 61.2 ± 23.3 *	-82.5 ± 30.4

Values are mean ± SD

\*: significantly different from Controls (\*:  $p < 0.05$ ; \*\*:  $p < 0.01$ ; \*\*\*  $p < 0.001$ )

GLS: global longitudinal strain. CS: circumferential strain.

**Table 4.** Myocardial work and Left ventricular mechanical dispersion

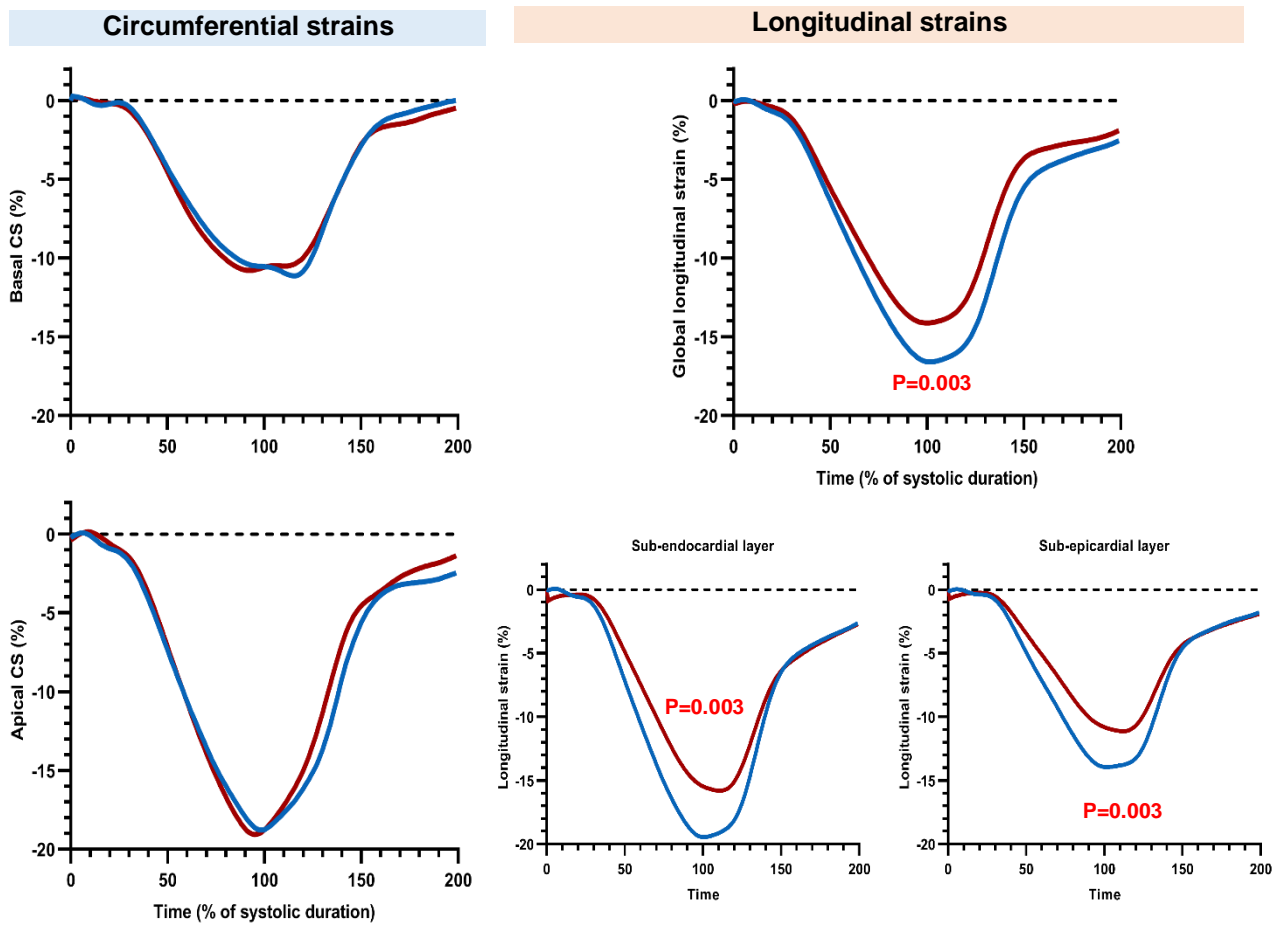
	<b>Patients (n = 16)</b>	<b>Controls (n=15)</b>
<b>Myocardial work</b>		
Constructive work (%.mmHg)	1834 ± 262	2042 ± 298 *
Wasted work (%.mmHg)	123 ± 72	91 ± 50
Global work efficiency (%)	0.93 ± 0.03	0.95 ± 0.02
<b>LV mechanical dispersion</b>		
Delta 1-18	237 ± 149	145 ± 50 *
SD <sub>18S</sub> (ms)	88 ± 33	58 ± 26 *

*Values are mean ± SD*

*\*: significantly different from Controls (\*: p<0.05)*

*SD: standard deviation*

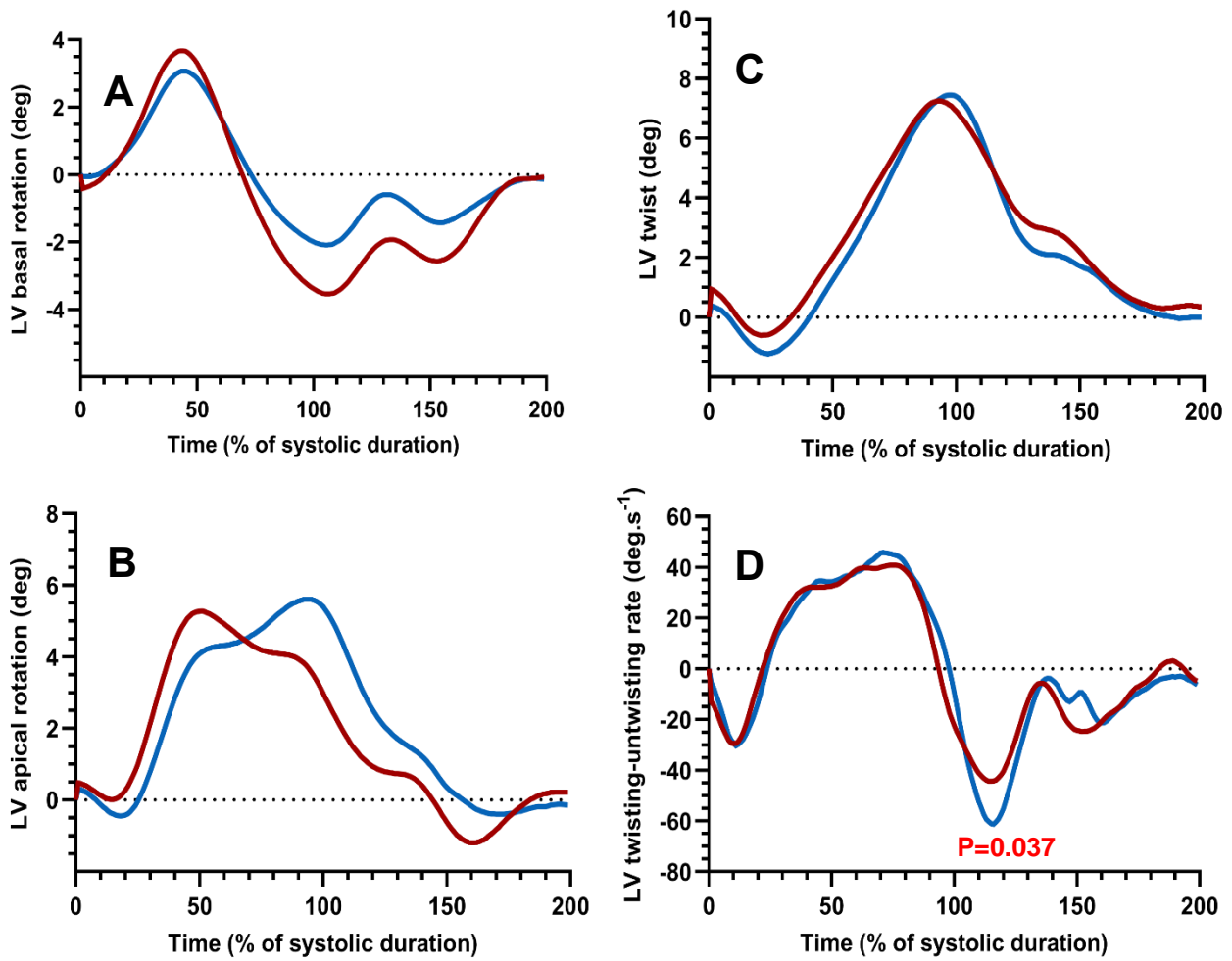
**Figure 1.** Longitudinal and circumferential strain



*Longitudinal strain and circumferential strains in CLS (red curve) and controls (blue curve). Circumferential strain is displaced as basal and apical segments. Longitudinal strains are displaced as global (GLS), sub-endocardial and sub-epicardial layers. Difference between groups:  $P < 0.05$*

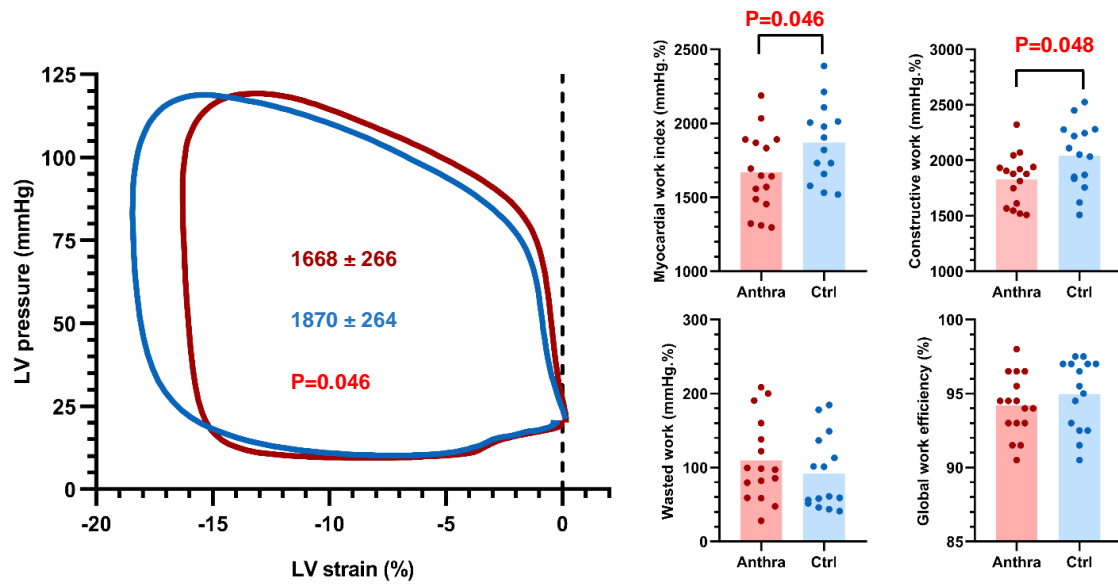


**Figure 2.** Left ventricular twisting mechanics



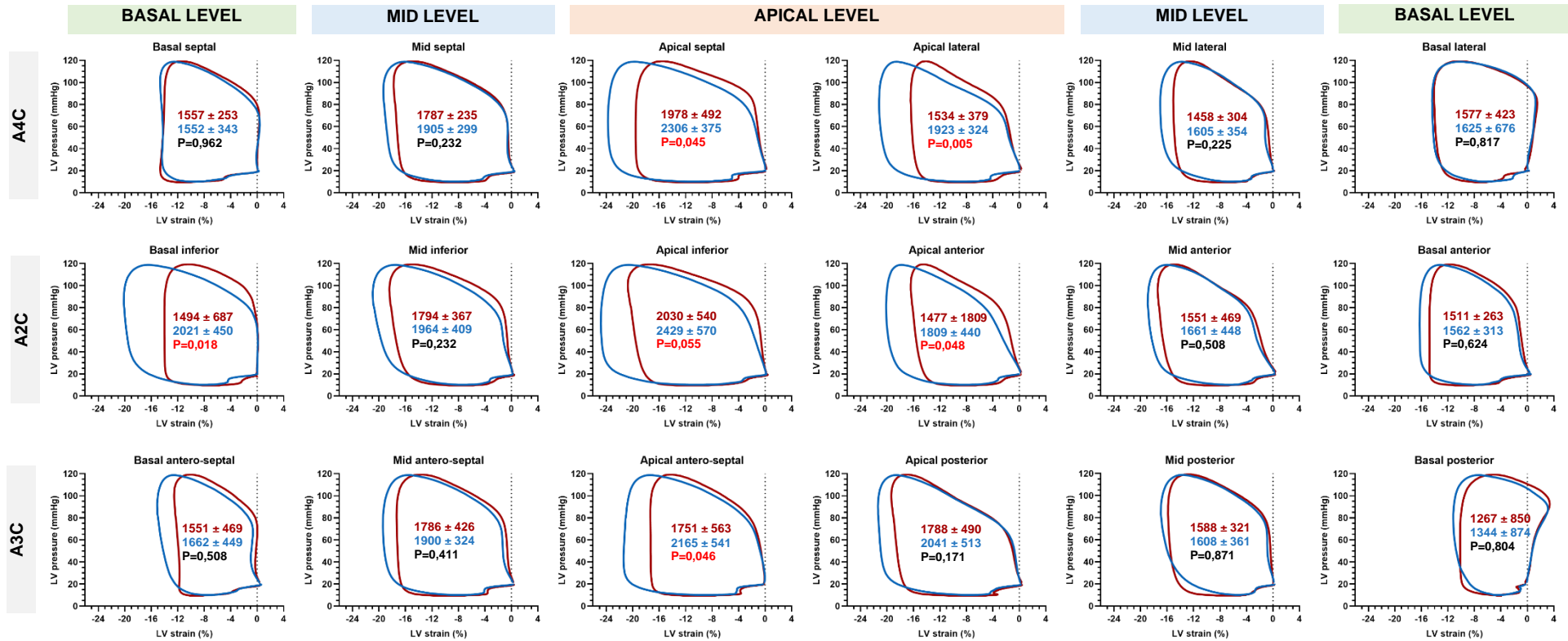
*Twist and untwist mechanisms in CLS (red curves) and controls (blue curves). A: Basal rotation, B: apical rotation and C: twist, function of time (% of systolic duration). D: Twist – untwist rate, function of time (% of systolic duration). Difference between groups:  $P < 0.05$*

**Figure 3.** Myocardial work and its components



*Non-invasively derived myocardial work indices from echocardiography. The left ventricle (LV) pressure–strain loop (PSL) is generated by incorporation of GLS, systolic blood pressure, and event timing of aortic and mitral valve opening and closing. The area of the pressure–strain curve then provides the global myocardial work index (MWI) (at the left side). Global myocardial work efficiency (MWE) is then obtained by dividing the global constructive myocardial work (MCW) by the sum of both MCW and global myocardial wasted work (MWW). All global values are derived from averages of their segmental values.*

**Figure 4.** Segmental Left ventricular Pressure-Strain loops



These 18 figures represent, for each line, the 3 (A3C), 2 (A2C), and 4 (A4C) chambers views, using the same coding with CLS (red curves) and controls (blue curves) on PSL. In each PSL segment, red  $P < 0.05$  indicates the existence of a significant difference with the corresponding segment of the control group.

**(Conseil national de l'ordre des médecins)**

**SERMENT D'HIPPOCRATE**

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.

Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés.

Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

JABER Mohamed

Signature

## **SERMENT D'HIPPOCRATE**

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES,  
je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans  
l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-  
dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront  
pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état  
ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants  
l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

JABER Mohamed

Signature