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RESEARCH ARTICLE

Assessment of Left Ventricular Diastolic Function in Patients with Diffuse Large B-cell Lymphoma after Anthracycline Chemotherapy by using Vector Flow Mapping

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Abstract:

Background:

Patients with diffuse large B-cell lymphoma (DLBCL) often experience a poor prognosis due to cardiac damage induced by anthracycline chemotherapy, with left ventricular diastolic dysfunction manifesting early. Vector Flow Mapping (VFM) is a novel technology, and its effectiveness in detecting left ventricular diastolic dysfunction following anthracycline chemotherapy remains unverified.

Object:

This study evaluates left ventricular diastolic function in DLBCL patients after anthracycline chemotherapy using vector flow mapping (VFM).

Materials and Methods:

We prospectively enrolled 54 DLBCL patients who had undergone anthracycline chemotherapy (receiving a minimum of 4 cycles) as the case group and 54 age- and sex-matched individuals as controls. VFM assessments were conducted in the case group pre-chemotherapy (T0), post-4 chemotherapy cycles (T4), and in the control group. Measurements included basal, middle, and apical segment energy loss (ELb, ELm, ELa) and intraventricular pressure differences (IVPDb, IVPDm, IVPDa) across four diastolic phases: isovolumic relaxation (D1), rapid filling (D2), slow filling (D3), and atrial contraction (D4).

Results:

When comparing parameters between the control and case groups at T0, no significant differences were observed in general data, conventional ultrasound parameters, and VFM parameters (all $P > 0.05$). From T0 to T4, ELa significantly increased throughout the diastole cycle (all $P < 0.05$); ELm increased only during D4 (all $P < 0.05$); and ELb increased during D1, D2, and D4 (all $P < 0.05$). All IVPD measurements (IVPDa, IVPDm, IVPDb) increased during D1 and D4 (all $P < 0.05$) but decreased during D2 and D3 (all $P < 0.05$). Significant positive correlations were identified between ELa-D4, IVPDa-D4, and parameters A, e', E/e,' and LAVI (all $r > 0.5$, all $P < 0.001$). Negative correlations were noted with E/A for ELa-D4 IVPDa-D4 (all $r < -0.5$, all $P < 0.001$). Positive correlations were observed for IVPDa-D1, IVPDa-D2 with E, E/e', and LAVI ($0.3<r<0.5$, all $P<0.001$).

Conclusion:

VFM parameters demonstrate a certain correlation with conventional diastolic function parameters and show promise in assessing left ventricular diastolic function. Furthermore, VFM parameters exhibit greater sensitivity to early diastolic function changes, suggesting that VFM could be a novel method for evaluating differences in left ventricular diastolic function in DLBCL patients before and after chemotherapy.

Keywords: Energy loss, Intraventricular pressure difference, Diffuse large B-cell lymphoma, Anthracycline, Vector flow mapping, Chemotherapy.

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1. INTRODUCTION

Lymphoma is one of the most common malignant tumors, with male Non-Hodgkin lymphoma (NHL) incidence and mortality rates ranking within the top ten for all malignancies. Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 30% of NHL cases [1]. Despite the advanced stage of diagnosis for many DLBCL patients, more than 60% respond effectively to R-CHOP chemotherapy. However, anthracyclines, a core component of R-CHOP, can cause side effects such as bone marrow suppression and cardiac impairment, often presenting initially as cardiac diastolic dysfunction [2]. It is suggested that diastolic dysfunction related to anthracycline treatment may occur earlier than previously thought [3]. Thus, early detection and management of anthracycline-induced left ventricular diastolic dysfunction are vital for reducing heart failure incidence.

Currently, noninvasive evaluation of the impact of anthracyclines on left ventricular diastolic function is not extensively documented. Cardiac catheterization, a conventional method for assessing diastolic function [4], is limited by its invasive nature and challenges in repeatability. Although Cardiac MRI provides high diagnostic accuracy for cardiac function changes [5], its use is restricted by numerous contraindications and significant costs. The 2016 guidelines from the American Society of Echocardiography and the European Society of Cardiovascular Imaging recommend using parameters such as E/A, E/e′, and LAVI to assess left ventricular diastolic function *via* transthoracic echocardiography (TTE) [6]. However, TTE's angle dependence can lead to less reproducible results and potential underestimation of cardiac function [7]. To date, a straightforward, noninvasive methodology for evaluating diastolic function has yet to be established [8]. Nonetheless, Vector flow mapping (VFM) emerges as a promising approach, utilizing intraventricular blood flow analysis to evaluate diastolic function [9]. VFM, grounded in color Doppler and speckle tracking principles, offers a noninvasive, repeatable, and user-friendly alternative, mitigating the angle dependence associated with TTE and effectively delineating left intraventricular blood flow dynamics.

Energy loss (EL) is an innovative hemodynamic parameter derived from VFM technology, indicating the thermal energy generated by friction between the viscous blood and the chamber wall, thereby effectively reflecting the blood flow dynamics based on the velocity vector. The intraventricular pressure difference (IVPD) is another novel metric obtained through VFM technology, incorporating the momentum conservation equation of fluid motion to quantify and visually represent the two-dimensional pressure field within the left chamber. These VFM parameters have been effectively applied in evaluating left ventricular diastolic function in patients with conditions such as diabetes [10], hypertension [11], and coronary artery stenosis [12]. In this study, we uniquely combined EL and IVPD to assess left ventricular diastolic function in DLBCL patients following anthracycline chemotherapy, potentially contributing to the prevention of heart failure.

2. MATERIALS AND METHODS

2.1. Patients

From September 2022 to November 2023, this study enrolled inpatients from the Department of Hematology and Oncology at the First Affiliated Hospital of Nanchang University. The case group included 54 pathologically confirmed DLBCL patients who received R-CHOP therapy (rituximab, cyclophosphamide, anthracyclines, vincristine, prednisone) for at least four cycles and had comprehensive clinical data. Exclusion criteria encompassed a history of heart disease, hypertension, hyperlipidemia, diabetes, other malignancies, abnormal liver or kidney function, rheumatic immune diseases, chest deformities, or any factors leading to unclear imaging. Additionally, 54 healthy volunteers, age- and sex-matched to the chemotherapy group, were selected as controls.

2.2. Ultrasound Equipment

The research utilized a Hitachi Aloka Lisendo 880 color Doppler ultrasound system with integrated VFM analysis software, operated with a phased array single crystal probe (frequency range: 1.0-5.0 MHz) and a Sun Tech Tango blood pressure monitor.

2.3. Measurements

General clinical data were collected for all participants, including gender, age, height, and weight. From these, the body mass index (BMI) [BMI (kg/m^2) = weight/height2] and body surface area (BSA) [BSA (m^2) = 0.0061× height + 0.0128× weight −0.1529] were calculated. We also gathered participants' past medical histories.

Before the examination, all subjects were connected to a synchronous ECG of limb leads and then positioned on their left side for the transthoracic echocardiography (TTE) examination. During TTE, we measured conventional diastolic function parameters: the E peak and A peak at the mitral valve orifice's early and late diastolic phases using pulse wave Doppler in the standard four-chamber view. In Tissue Doppler Imaging (TDI) mode, we obtained the mean values of e′ and a′, the early and late diastolic peak velocities, at the annular ventricular septal and lateral walls of the mitral valve. From these, we calculated the ratios E/A, e′/a′, and E/e′. The ejection fraction (EF) was determined using the Simpson method, and the left atrial volume (LAV) was measured to calculate the left atrial volume index (LAVI = LAV/BSA). Dynamic images capturing the full spectrum of left ventricular blood flow across more than three cardiac cycles were saved for subsequent in-machine VFM analysis in a three-chamber view.

A Time Flow Curve (TFC) was generated from calculations performed 2 cm above the mitral valve. The cardiac diastolic cycle was segmented into four phases: isovolumetric diastolic periods (D1), rapid filling period (D2), slow filling period (D3), and atrial systolic period (D4) integrating TFC, ECG, and valve dynamics (Fig. **1**). For each phase, the left ventricular region of interest was identified, and measurements of left ventricular energy loss (EL) and intraventricular pressure difference (IVPD) were recorded. This included EL and IVPD for basal (ELb, IVPDb), middle (ELm, IVPDm), and apical (ELa, IVPDa) segments (Fig. **2**).

Skilled sonographers conducted all echocardiographic assessments. The reported values for VFM and echocardiographic parameters represent averages over three consecutive cardiac cycles. Blood pressure was consistently measured by trained nurses during each hospital visit, using a mercury sphygmomanometer on the patient's right arm after at least 5 min of rest in a seated position. Height and weight were recorded with patients in light clothing and without shoes.

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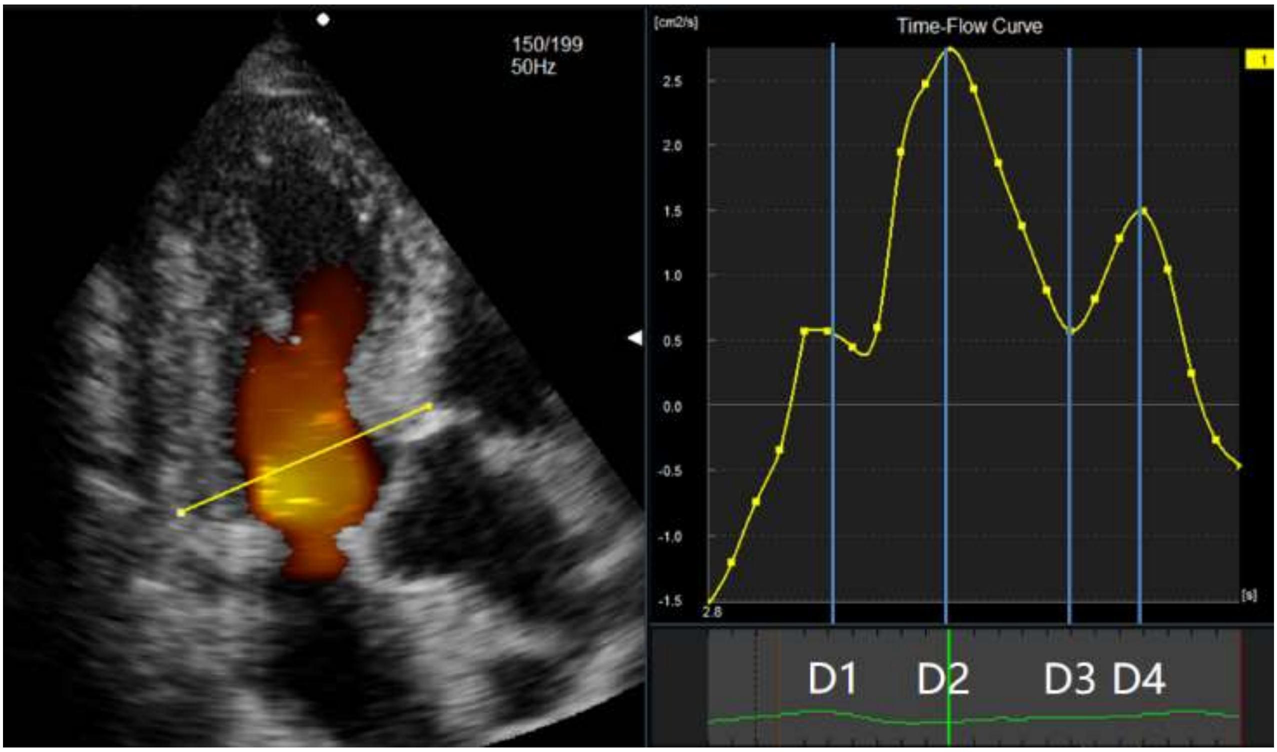
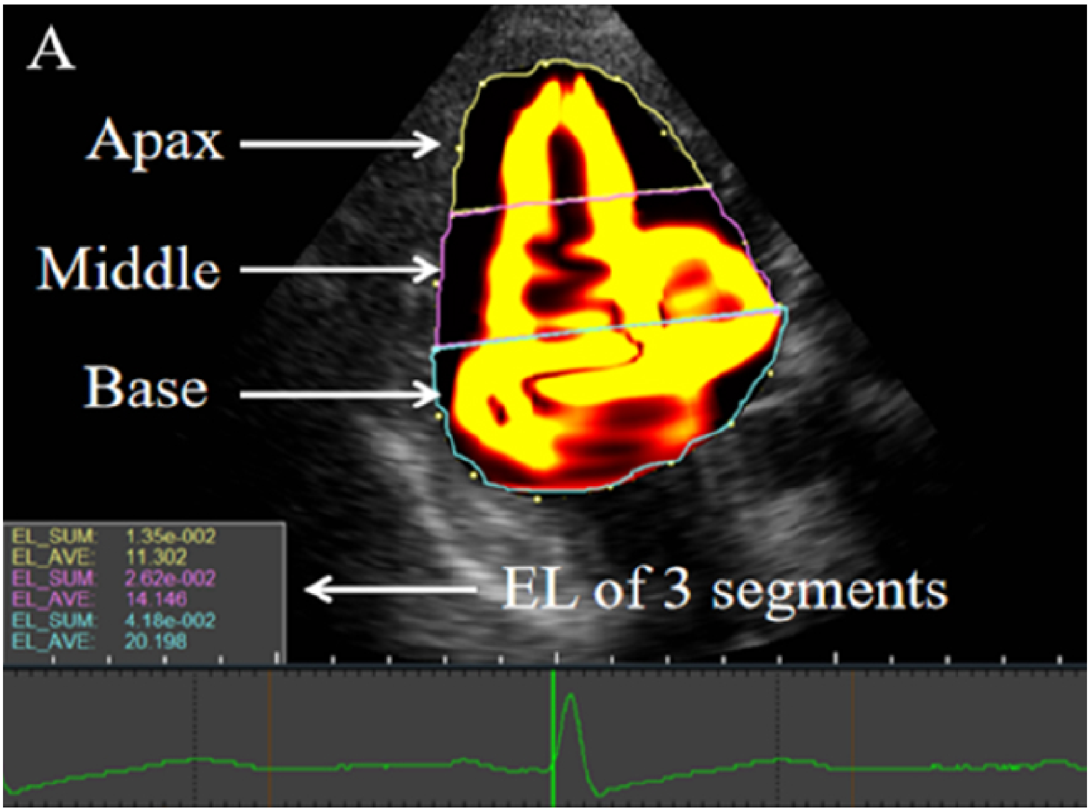


Fig. (1). The four phases of the cardiac cycle. The time-flow curve during diastole. D1=isovolumic relaxation; D2= rapid filling; D3=slow filling. D4=atrial contraction.



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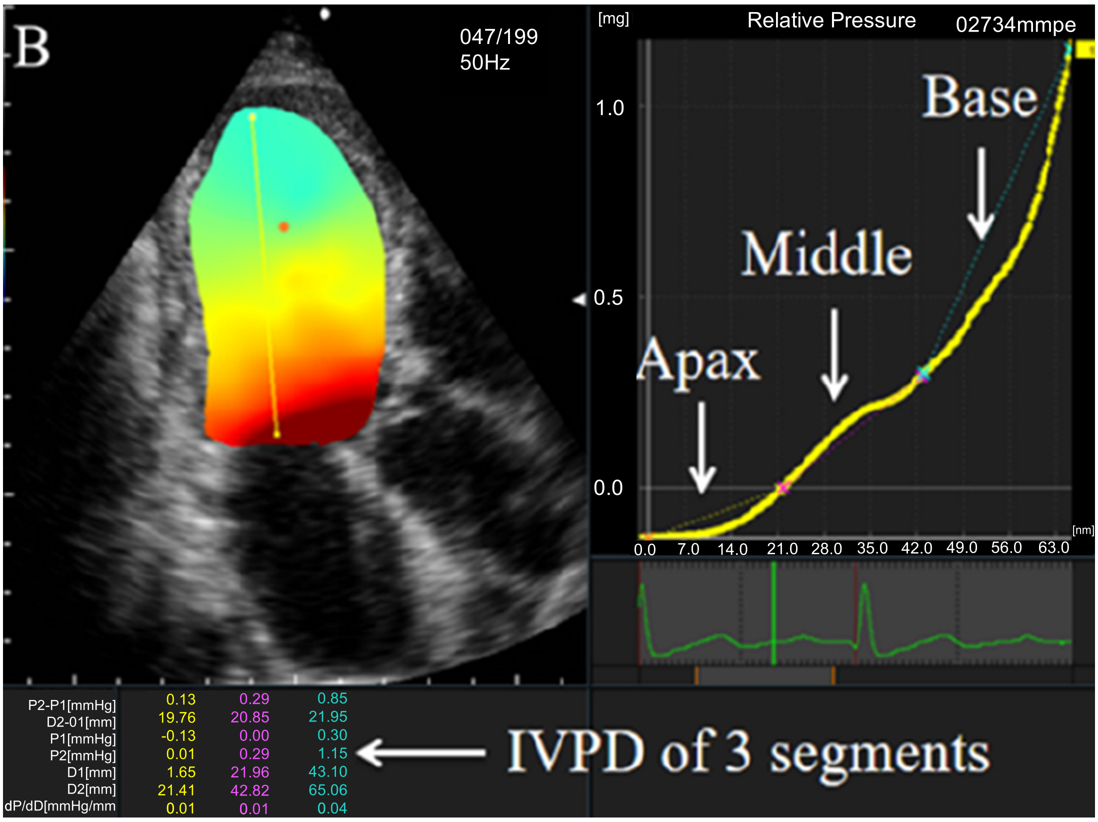

Fig. (2). The ultrasound measurements of EL (**A**) and IVPD (**B**) using VFM. (**A**) The LV was divided into three segments. EL_AVE is the averaged EL. (**B**) P2-P1 is the IVPD.

2.4. Statistical Analysis

Data were analyzed using the SPSS 27.0 software package (SPSS Inc., Chicago, IL, USA). Normally distributed data are presented as means ± standard deviation. The independent samples t-test was used to compare case groups with control groups, while the paired samples t-test facilitated intra-group comparisons within case groups pre- and post-chemotherapy. Pearson correlation tests analyzed correlations between VFM parameters and echocardiographic diastolic function parameters. A p-value < 0.05 was deemed statistically significant, with p-values derived from two-tailed tests.

3. RESULTS

3.1. Demographic Characteristics and Conventional Echocardiography

The study involved 54 DLBCL patients (case group) and 54 healthy individuals (control group). No statistically significant differences were noted in age, sex, weight, BMI, BSA, and blood pressure between the two groups (P > 0.05, Table **1**). Similarly, echocardiographic parameters did not show significant differences between groups (all P > 0.05, Table **2**). However, significant differences were observed in echocardiographic parameters such as E/e' (8.52±1.68 *VS* 9.45±1.45) and LAVI (29.16±4.54 *VS* 33.12±4.19) between the case group T0 and T4 (both P < 0.05, Table **2**).

3.2. Vector Flow Mapping

No significant differences in EL and IVPD across the three segments were found between the case and control groups during all four phases (all P > 0.05). Yet, in the case group from T0 to T4, ELa increased throughout the diastole cycle (all P < 0.05), ELm rose only during D4 (5.97 ± 1.76 *vs* 6.74 ± 2.52, P < 0.05), and ELb escalated during D1, D2, and D4 (all P < 0.05) (Fig. **3**). Furthermore, all IVPD measurements (IVPDa, IVPDm, IVPDb) increased during D1 and D4 (P < 0.05, Fig. **3**) but decreased during D2 and D3 (P < 0.05) (Table **3**).

Table 1. Demographic characteristics of the study subjects.

Variables	Control Group	Case Group	P value
Age (years)	55.7±10.1	56.2±10.3	0.436
Female	18(33.3%)	18(33.3%)	>0.05
Male	36(66.7%)	36(66.7%)	>0.05
Weight (kg)	51±9.6	50±8.9	0.346
BMI (kg/m^2)	23±5.3	22±6.1	0.231

(Table 1) contd.....

Variables	Control Group	Case Group	P value
BSA (m^2)	1.66±0.23	1.67±0.28	0.196
SBP(mmHg)	119±15.3	117±16.1	0.276
DBP(mmHg)	69±10.2	67±9.5	0.283

Abbreviations: BMI: body mass index, BSA: body surface area, SBP: systolic blood pressure, DBP: diastolic blood pressure.

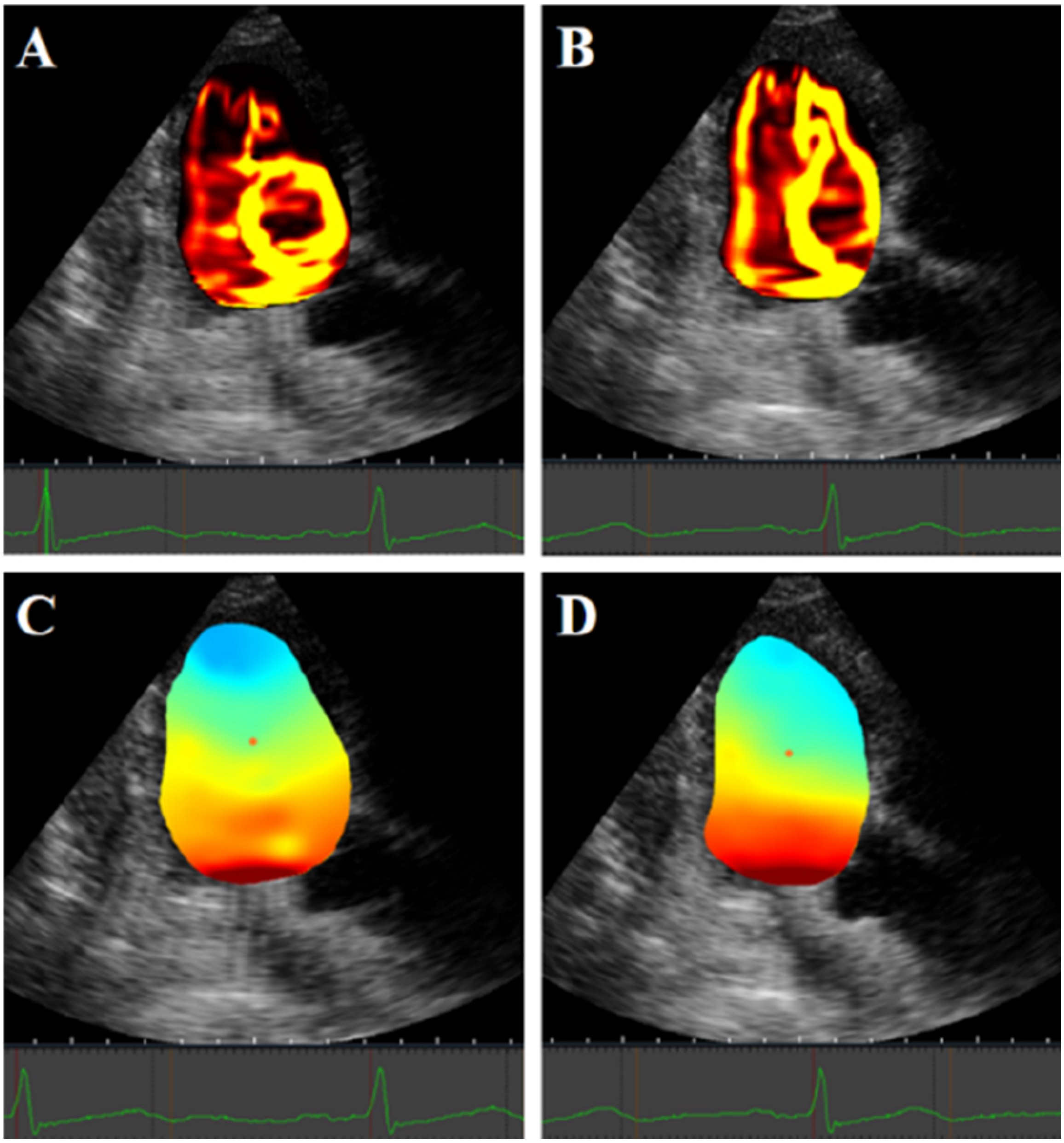

Fig. (3). 65-year-old male DLBCL patient, the EL during the D4 in pre-chemotherapy (**A**) and post-4 chemotherapy (**B**). After chemotherapy, the EL gradually increases compared with pre-chemotherapy (The yellow area shows the range of energy loss). The IVPD during D4 in pre-chemotherapy (**C**) and post-4 chemotherapy (**D**). After chemotherapy, the IVPD gradually increases compared with pre-chemotherapy. (blue-red indicates low pressure-high pressure).

Table 2. Conventional echocardiographic parameters.

Variables	Control Group	Case Group T0	Case Group T4	P1 value	P2 value
E	75.47±9.42	76.37±8.65	75.08±8.30	0.613	0.807
A	77.23±12.52	76.45±11.76	80.14±10.09	0.873	0.295
E/A	1.00±0.22	0.99±0.26	0.94±0.27	0.961	0.453

(Table 2) contd.....

Variables	Control Group	Case Group T0	Case Group T4	P1 value	P2 value
e’	9.15±1.82	9.18±1.77	8.53±1.12	0.765	0.067
E/e’	8.53±1.76	8.52±1.68	9.45±1.45	0.879	0.031
LAVI	29.56±4.12	29.16±4.54	33.12±4.19	0.254	0.015
EF (%)	63.34±5.42	62.45±4.82	59.23±6.42	0.546	0.427

Abbreviations: E: early filling, A: late filling, LAVI: left atrial volume index, EF: ejection fraction.

Table 3. LV EL and IVPD of different parts in four phases.

Variables	Control Group	Case Group T0	Case Group T4	P1value	P2 value
EL (J/ms)	-	-	-	-	-
ELa-D1	1.05±0.17	1.01±0.22	1.22±0.19	0.787	0.021
ELa-D2	7.36±2.52	7.51±2.49	7.95±2.43	0.764	0.047
ELa-D3	3.01±1.64	3.03±1.79	3.61±2.02	0.955	0.014
ELa-D4	5.66±1.49	5.69±1.52	6.44±2.31	0.929	0.020
ELm-D1	0.71±0.13	0.63±0.17	0.71±0.16	0.528	0.076
ELm-D2	6.93±2.23	6.91±2.26	7.45±2.34	0.956	0.077
ELm-D3	3.23±2.15	2.97±1.75	3.22±1.86	0.497	0.117
ELm-D4	5.96±1.71	5.97±1.76	6.74±2.52	0.956	0.029
ELb-D1	0.94±0.23	0.88±0.32	0.93±0.29	0.701	0.371
ELb-D2	7.34±2.53	7.40±2.61	8.73±3.15	0.911	0.005
ELb-D3	3.19±1.08	3.20±1.19	3.52±1.22	0.984	0.178
ELb-D4	6.27±1.76	6.31±1.86	7.28±2.79	0.899	0.014
IVPD (mmHg)	-	-	-	-	-
IVPDa-D1	0.062±0.029	0.065±0.022	0.079±0.033	0.747	0.044
IVPDa-D2	0.164±0.052	0.167±0.053	0.121±0.052	0.792	<0.001
IVPDa-D3	-0.149±0.066	-0.153±0.071	-1.33±0.064	0.755	0.002
IVPDa-D4	0.122±0.050	0.118±0.040	0.157±0.067	0.645	<0.001
IVPDm-D1	0.435±0.128	0.443±0.127	0.350±0.168	0.767	<0.001
IVPDm-D2	0.543±0.170	0.551±0.175	0.316±0.148	0.813	<0.001
IVPDm-D3	-0.506±0.122	-0.515±0.235	-0.366±0.182	0.436	<0.001
IVPDm-D4	0.400±0.168	0.385±0.132	0.406±0.177	0.618	0.013
IVPDb-D1	0.522±0.153	0.531±0.152	0.564±0.199	0.765	<0.001
IVPDb-D2	0.651±0.204	0.660±0.210	0.751±0.174	0.815	<0.001
IVPDb-D3	-0.601±0.263	-0.619±0.282	-0.497±0.217	0.735	<0.001
IVPDb-D4	0.480±0.201	0.462±0.158	0.606±0.210	0.611	<0.001

Note: P1: Independent sample t-tests between the case group and control group.
P2: Paired sample t-test comparisons pre- and post-chemotherapy in the case group.

Table 4. Correlation analysis between VFM parameters of the apical segment and diastolic function parameters in echocardiography.

Variables	Ela (J/ms)				IVPDa (mmHg)			
	D1	D2	D3	D4	D1	D2	D3	D4
E	0.227	0.225	0.217	0.201	0.445*	0.474*	-0.217	-0.207
A	0.134	-0.121	0.126	0.553*	0.285	-0.224	0.293	0.627*
E/A	-0.081	-0.068	-0.151	-0.567*	0.208	0.244	0.254	-0.688*
e’	-0.188	-0.115	-0.032	0.598*	0.294	0.291	-0.217	0.522*
E/ e’	0.111	0.066	0.013	0.564*	0.368*	0.371*	-0.262	0.728*
LAVI	0.050	0.123	0.064	0.593*	0.445*	0.364*	-0.220	0.674*

Note: *P<0.001

3.3. Correlation Analysis

Significant positive correlations were identified between ELa-D4, IVPDa-D4, and the parameters A, e', E/e', and LAVI (r=0.553, r=0.598, r=0.564, r=0.593; r=0.627, r=0.522, r=0.728, r=0.674; all P <0.001), while negative correlations were observed with E/A for ELa-D4, IVPDa-D4 (r=-0.567, r=-0.688; all P <0.001). Additionally, positive correlations were observed for IVPDa-D1 and IVPDa-D2 with E, E/e', and

LAVI (r=0.545, r=0.368, r=0.345; r=0.574, r=0.371, r=0.364; P < 0.001) (Table **4**).

4. DISCUSSION

The five-year survival rate for DLBCL patients undergoing R-CHOP chemotherapy, which predominantly includes anthracycline drugs, has markedly improved [13]. Nevertheless, anthracyclines are associated with a spectrum of side effects that negatively impact prognosis, particularly concerning cardiac function impairment [14]. Anthracycline drugs disrupt DNA biosynthesis through DNA intercalation and can cause DNA damage by inhibiting topoisomerase, resulting in myocardial cell injury and diminished cardiac function [15]. Evidence suggests that anthracyclines significantly affect cardiac diastolic function in patients with malignant tumors [16, 17]. This underscores the urgent need for innovative studies to devise more accessible and effective diagnostic approaches for evaluating left ventricular diastolic function after anthracycline chemotherapy, thereby enhancing support for clinical decision-making.

In our study, no significant differences were observed in demographic characteristics, echocardiogram parameters, or VFM parameters between the case and control groups. This indicates that early-stage DLBCL does not markedly affect cardiac function. Recent research suggests that treatment approaches for early DLBCL have a more pronounced impact on cardiac function than the disease itself [18]. In the case group, LVEF remained unchanged during chemotherapy, while changes in LAVI, e', E/e,' EL, and IVPD were statistically significant. This suggests that anthracyclines predominantly affect left ventricular diastolic function rather than systolic function [19]. Anthracyclines damage myocardial cell mitochondria through oxygen-free radical damage, leading to an energy deficit in the Ca^{2+} pumps of myocardial cells, compensatory collagen fiber proliferation, and collagen deposition in the extracellular matrix, thus reducing myocardial compliance [20]. Consequently, anthracycline-induced reductions in left ventricular compliance diminish left ventricular twists and torsion, resulting in diastolic dysfunction [21]. Early detection of diastolic function changes enables strategies to mitigate cardiac toxicity, such as adjusting chemotherapy regimens or reducing anthracycline dosage [22] and the potential use of Dexrazoxane to prevent or lessen cardiotoxicity in patients receiving anthracyclines [23].

Microvascular dysfunction and improper Ca^{2+} interactions with myofilaments during diastole are crucial in diastolic dysfunction, leading to diastolic restriction of the left ventricle. The increases in LAVI and E/e' in our study support this observation. Anthracyclines induce endothelial dysfunction in cancer patients, reduce the expression and Ca^{2+} sequestering function of sarcoplasmic Ca^{2+}-ATPase, and promote calcium-dependent protease degradation of titin, essential for myocardial relaxation [24]. This process significantly raises left ventricular stiffness, negatively impacting myocardial relaxation. Moreover, diminished left ventricular diastolic function increases left atrial preload. According to the Frank-Starling mechanism, this boosts left atrial contractile force, modifies the atrioventricular pressure gradient, and heightens atrioventricular blood flow velocity, altering left ventricular late diastolic function and causing significant shifts in EL and IVPD during D4. Additionally, anthracycline-induced focal myocardial degeneration disrupts left ventricular flow during atrial contraction, increasing EL [25]. From T0 to T4 in the case group, post-chemotherapy blood flow patterns became abnormal, with EL and IVPD generally trending upward. During D3, IVPD turns negative and decreases post-chemotherapy, reflecting increased cardiac stiffness and reduced relaxation. This leads to blood accumulation at the apex and a higher apex pressure than at the basal segment.

The basal segment of the left ventricle receives a more adequate blood supply compared to the middle and apical segments. Yet, it is less responsive to changes in blood flow [26] than the apical segments, aligning with our findings. Heart movement relies on forces acting in different directions within the basal and apical segments, the latter being more significant. Impaired diastolic function in ventricular muscles disrupts the formation of an effective pressure gradient in the apical segment, reducing its influence on blood flow direction [27]. The basal segment compensates for this, mitigating hemodynamic effects in the middle and apical segments, which results in more pronounced changes in EL and IVPD in the apical segments, as observed in our study. E/e′ is recognized as correlating with cardiac diastolic function. Our research identified a positive correlation between diastolic ELa and E/e′ during D4, suggesting that an elevated E/e′ indicates increased left ventricular filling pressure during diastole. High-velocity blood flow significantly raises EL, and Ela-D4 could be a vital parameter for assessing left ventricular diastolic function [28]. Left ventricular untwisting, crucial for relaxation and suction, drives early diastolic blood flow stemming from the atrioventricular pressure difference gradient [29]. The larger this pressure gradient, the higher the blood flow velocity during early diastole. Our findings show a positive correlation between E and IVPDa-D1, IVPDa-D2, and between A and IVPDa-D4. The correlation analysis between VFM and echocardiographic parameters in our study revealed a strong association between ELa, IVPDa, and diastolic function parameters such as E/A, e', E/e,' and LAVI, further substantiating the effectiveness of VFM technology in assessing alterations in left ventricular diastolic function [30].

Our study has several limitations. The relatively small sample size renders the results preliminary and highlights the need for larger studies to obtain more comprehensive insights. The complexity of blood flow in the human heart is three-dimensional and dynamic; however, VFM analyzes only two-dimensional blood flow changes, which introduces certain constraints. After four chemotherapy cycles, some DLBCL patients changed their chemotherapy regimen due to alterations in their clinical status. This study did not examine the changes in cardiac function parameters following subsequent chemotherapy cycles.

CONCLUSİON

In conclusion, VFM parameters correlate with traditional diastolic function parameters and show promise in assessing left ventricular diastolic function. Moreover, VFM parameters are particularly sensitive to early diastolic function alterations, positioning VFM as a potential new technique for assessing changes in left ventricular diastolic function in DLBCL patients before and after chemotherapy.

AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to itssubmission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

TDI	=	Tissue Doppler Imaging
ECG	=	Electrocardiogram
VFM	=	Vector flow mapping

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The ethics committee of the First Affiliated Hospital of Nanchang University and Clinical Medicine Ethics Review approved this study. The number of Ethics is (2023)CDYFYYLK (01-049)

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the Declaration of Helsinki revised by WMA, amended in October 2013

STANDARDS OF REPORTING

STROBE guidelines were followed.

CONSENT FOR PUBLICATION

Written informed consent was obtained from all participants.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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