COMPARATIVESTUDYBETWEEN TWO-DIMENSIONAL AND REAL TIME THREE-DIMENSIONAL ECHOCARDIOGRAPHYFORASSESSMENTOFLEFT VENTRICULARSYSTOLIC FUNCTION IN LEFTBUNDLEBRANCHBLOCK POPULATION.

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Aims:
Evaluatetheroleof systolic dyssynchrony index (SDI), measured by real time three dimensional echocardiography (RT3DE), in assessment of LVEF and left ventricular volumes accurately in patients with LBBB.

Methods and Results: In this case–control study, we included 65 enrolled participants with LBBB either with normal LVEF or depressed LV systolic function with isolated WMAs of LBBB only . Left ventricular ejection fraction (LVEF) and left ventricular volumes were assessed by 2DE (modified Simpson's method) and RT3DE (four beats full volume acquisition and sequential analysis) echocardiography and the effect of SDI on results was evaluated. In patients with SDI ≥7%, LVEF measurements were significantly different (45.61% [34%-66 %] vs 37.18% [24 %– 55.6 %], P value<.0001) between 2DE and RT3DE respectively. In patients with SDI < 7%, no significant differences between two modalities in terms of LVEF measurements (46.73% [35% -57 %] vs 44.58% [33.4 % –55.6%], P = .158) between 2DE and RT3DE respectively. LV diastolic volumes were not significantly different while systolic volumes were higher by RT3DE, and this results were mainly with higher SDI (more than or equal 7)

Conclusion:InpatientswithLBBBandhighSDI(≥7%),LVEFvalueswerelower andsystolicvolumeswerehigher byreal time three dimensionalechocardiographycomparedtotwo dimensionalechocardiography.

Keywords

leftbundlebranchblock,leftventricularejectionfraction,systolicdyssynchronyindex,three-dimensionaltransthoracicechocardiography

1 |INTRODUCTION

Leftventricularejectionfraction(LVEF) assessment in LBBB might be chanllenging to many echocardipgraphersbut itsamajordeterminantofclinicaloutcomeinthis population ;therefore,accuratemeasurementofLVEFisessential,thebiplanemethodofdisks(modifiedSimpson'smethod) and tissue doppler are themost widely usedandrecommendedmethod for assessing LVEF & SDI respectivelybytherecentreportsofAmericanSocietyofEchocardiography (ASE) andEuropeanAssociationofCardiovascularImaging(EACVI).[1]

Two-dimensional(2D) basedechocardiographicmeasurementofLVEF has some disadvantages like apical foreshortening , inability to avoid assumptions ofventricular geometry and inappropriate asseeement of ventricular volumes especially with wall motion abnormalities like those of LBBB .[2] These limitations could be overcome by realtimethree-dimensionalechocardiography(RT3DE).Asweknowthat,RT3DE is compatible with cardiac magnetic resonance, which is stillthe gold standard method, and it gives more accurate results than2DEintermsofmeasuringLVEFandLVvolumes[3].

Althoughitisnotarealregionalwall-motionabnormality,LBBB,mimicsthisentity becauseofdyssynchronizedcontractionof LVduetoabnormalityinthesequenceofactivation of ventricular bundle branches whichresultsinnoncoordinatedcontractionofinterventricularseptumandLVposterolateralwall(earlyactivationofinterventricularseptumposteriorly -septalbeaking-followedbyaparadoxicalanteriormotionlaterinsystolicejectionphase)[4], moreover ,it leads to „rebound" stretching of the septum during first part of the LVejection despite the fact that septalmyofiber stress still rising. Most of theLV ejection is done by the lateral regions which in long term causing theirhypertrophy[5] recentely after widenspread of TAVI(transcatheter aortic valve implantation) and the common iatrogenic result of LBBB which is proved to be the strongest predictor independently of the mortality at the follow up [6], and recent changes of indication of CRT (cardiac

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resynchronization therapy)[7]givingaparticularattentiontothisconductionabnormality.

Wehypothesizedthatthemagnitudeofdyssynchronymighthavea critical role in measurement LVEF correctly in patients with LBBB;therefore,wecomparedLVvolumesandLVEFmeasuredby2DEandRT3DEinthispopulation.

2 |METHODS

2.1 |STUDYPOPULATION

We enrolled 65 participants with LBBB who have presented to ourcardiology outpatient clinic and ER in cardiothoracic Minia university hospital in the period between December 2018 and October 2020 and performed 2DE and RT3DE at the same session. Weexcluded any all patients with (poor imagequality,severeheartvalvedisease,atrialfibrillation, pulmonary hypertension, , prosthetic heart valveand patients with echocardiographic wall motion abnormalities of LV other than those of LBBB were also excluded. Informed consents wereobtained from all participants, and this study was approved by ourMinia university ethicscommittee.

2.2 |Echocardiographyprotocolsandimage acquisition:

WeusedPhilipsiE33echocardiographymachinewithax matrixarray ultrasonographic transducer (X5.1 transducer; Philips MedicalSystems, USA launches in 2010) for conventional 2DE and RT3DE. WeperformedthemodifiedSimpson’smethodtomeasureLVEF,leftventricular end-systolic volume (LVESV) and left ventricular end-diastolicvolume (LVEDV) with all volumes indexed to BSA (measured with mosteller's formula) to eliminate effect of body mass in 2DE as described in EACVI.[1] Full volume fourbeats RT3DE images were obtained from apical four-chamber view.We firstly managed for optimal gain and compress, sector width anddepth at two-dimensional setting and switched to xPlane imaging todetect the quality of endocardial borders at orthogonalview. Afterobtaining a satisfactory image which included all segments of myocardium clearly as shown in figure (1), the patients were asked for breath-holding to prevent stitching artifacts and then we acquired four beats full volumesin a pyramidal scan[8]. Acquisition of each subvolume was ECG gatedand regular four consequent R-wave (by excluding premature beats)were used to build a full volume dataset. Elevation and lateral widthofimageswereoptimizedtoreachaframeratein the range of 25 to 34 fps)[9]. Measurementsof volumes and EF were performed postprocess using Qlab software(Version9.0;PhilipsMedicalSystems) which included in our echocardiographic machine and another external computer station.thenwe analyzedtwentyrandomlyselecteddataonemoretime

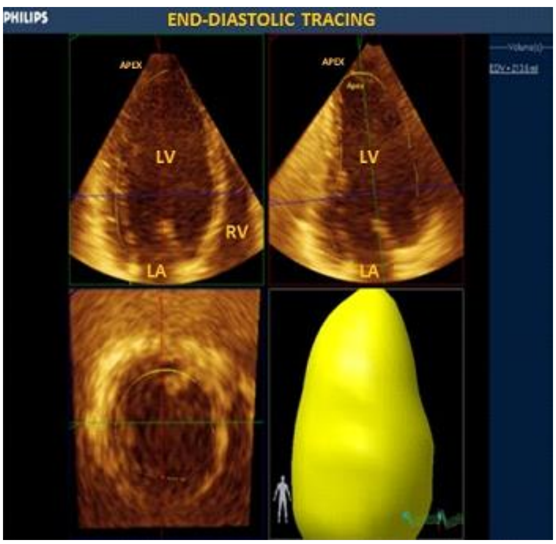

FIGURE1 End-diastolicendocardialtracingsinfull volumeanalysis

to detect intra-observer variability. End-diastole was defined as thefirstframeaftermitralvalveclosure,andend-systolewasdefinedasthefirstframeafteraorticvalveclosure.Butvisuallycorrectedinsomeindividualsoneframeforwardorbackwardbasedonthesize of LV cavity. Before automatic border definition, we adjustedtransverse plane (at the level of papillary muscles) and saggital plane (from themidline of mitral annulus to apex). Automatic border definition was performed by applying four points: septal, lateral, anterior,inferior at the level of mitral valve annulus, and the 5th point was apical in either A2C or A4C[8]. Border definitions were manually modified in most of cases by including papillary muscles and trabeculations as parts of LV cavity (Figure 2). We performed sequenceanalysisandcheckedforcorrectborderdetectionframe-by-frame.If the result was not satisfactory, we reanalyzed with another acquiredfullvolumedataset.Leftventricularend-diastolicvolume(LVEDV), LVESV, LVEF, and 16 segments SDI were obtained at theend of analysis which was shown as a report page in the software(Figure 3). Left ventricular volumes were also indexed to BSA.

2.3 |Statisticalanalysis

SPSS20.0(SPSS,Chicago,IL,USA)wasusedforstatisticalanalysis.TheKolmogorov–Smirnovtestwasappliedtodeterminethenormaldistribu-tionsofdatasets and paired t-test was used in comparison between two paired groups.Categoricalvariablesweredemonstratedasnumberandpercentage.Continuousvariablesweredemonstratedasmean±SD whennormallydistributedwhilenonparametricvariablesweresshownasmedianandtherangesof25%–75%quartiles.Wetestedthesignificance of differences between two echocardiographic modalities intermsofmeasuredLVEF,LVEDVIandLVESVIbyWilcoxonsigned-ranktest.Intra/inter-observeragreementswereanalyzedbyKappatest.The

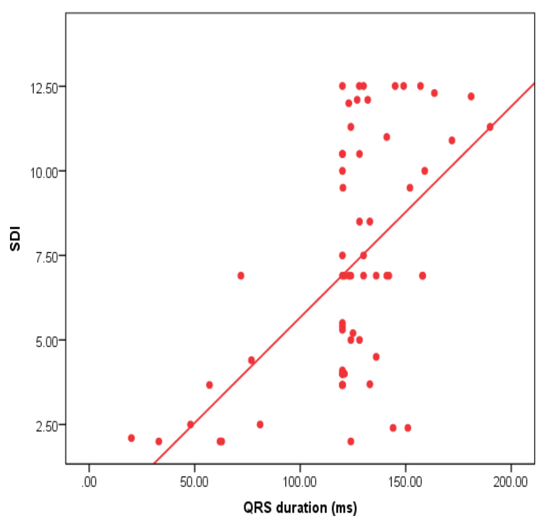

Figure (2) Positive linear relationship between SDI & QRS duration

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correlationbetweenQRSdurationandSDIwasanalyzedbySpearman'stestafteralinearcorrelationshown.Two-tailed*P*-valuesof<.05wereacceptedstatisticallysignificant.

3 |RESULTS

Baseline cardiovascular risk factors and echocardiographic param-etersofparticipantsshowninTable1.Patientswerebetween36and 82 years old, and 26 patients were female. thirtypatientshadLVEFequalormorethan50%accordingto2Dmeasurements while others had less than 50%.

InpatientswithSDI≥7%(accordingto16segmentsmodel,n=28),LVEFwasoverestimatedby2DEcomparedtoRT3DE(45.61%[34.00-66.00]vs37.18%[24.00-55.60],*P*<.001).Inpatientswith SDI <7% (n = 37), there were no significant difference between LVEFmeasurements(46.73%[35.00-57.00]vs44.58%[33.40-55.60], *P*=.158)calculatedby2Dand3Dechocardiography,respectively.LVdiastolic volume indices were not different between two modalitieswhile systolic volume indices were underestimated by 2DE, and thedifferencesweremorepronouncedwhenSDI≥7%(Table2).

QRSdurationswerepositivelycorrelatedwithSDI(r=.559,P < .001).Perfectinter-observer(k = 0.91)andintra-observer(k=0.93)agreementswereachieved.

Figure (3) report page after sequential analysis with 16 segments SDI highlighted in orange box

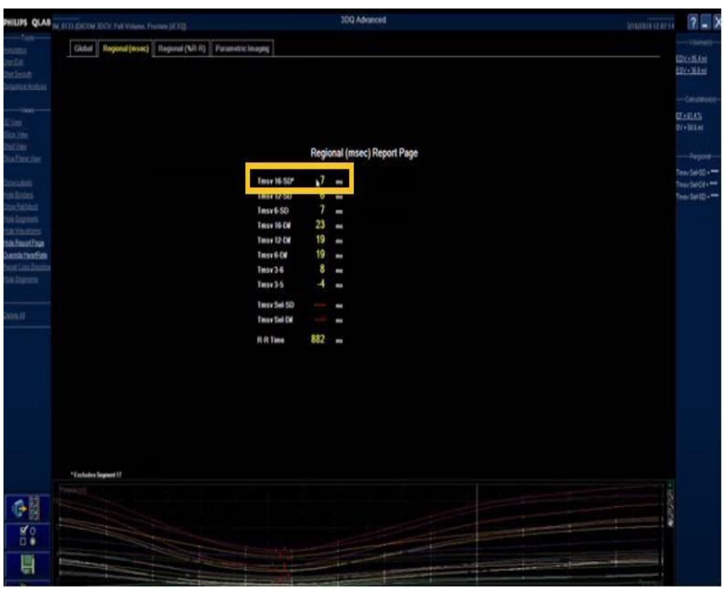

TABLE1 Baselinecharacteristicsandechocardiographicfindings

Parameter	Patients
Baselinecharacteristics	
Age(mean,range)	54.97(±13.83)
Female(n,%)	26(40)
Height(cm)	161.65(±10.78)
Weight(kg)	73.69(±7.20)
QRSduration(ms)	130.26(120-159)
Heartrate	76.83(±12.10)
HT(n,%)	25(38.5)
DM(n,%)	28(43.1)
Smoking(n,%)	29 (44.6)
Echocardiography	
LVEDD(mm)	49.48 (44.00–54.00)
LVESD (mm)	34.58(28.00-40.00)
LA diameter (mm)	37.69(±3.68)
LVEDVI (RT3DE)	60.56(47.00-91.83)
LVEDVI(2DE)	59.10(43.00-93.85)
LVESVI(2DE)	27.39(17.27-65.60)
LVESVI(RT3DE)	31.39(20.52-63.00)
LVEF(2DE)	46.25(46.00-66.00)
LVEF(RT3DE)	41.39(24.00-55.60)
e/a	0.89(0.70-1.10)
e/e’lateral	7.94(5.90-10.56)
EDT(ms)	163.66(±55.83)
IVRT(ms)	111.21(±24.32)
SDI(%)(RT3DE)	7.93(3.67–12.51)

LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricularend-systolicdiameter;LA=leftatrium; LVEDVI=leftventricularend-diastolicvolume indexed to BSA;LVESVI=leftventricularend-systolicvolume indexed to BSA;LVEF=leftventricular ejection fraction; DT = deceleration time (E-wave); IVRT = iso-volumetricrelaxationtime;SDI=systolicdyssynchronyindex.

TABLE 2 LVEF and LV volumes measured by 2DE and RT3DE

	LVEF(%) 2DE–RT3DE	LVEDVI (mL/m^2) 2DE–RT3DE	LVESVI (mL/m^2) 2DE–RT3DE
SDI			
≥7%	45.61(34.00-66.00)–37.18(24.00-55.60)	68.10(51.66-93.85)–70.34(51.00-91.83)	33.33(21.00-65.60)–43.31(28.00-63.00)
P-value	.000	.501	.002
SDI			
<7%	46.73(35.00-57.00)–44.58(33.40-55.60)	52.28(43.00-58.00)–53.43(47.00–63.00)	22.89(17.27-28.51)–23.89(20.52–49.65)
P-value	.158	.329	.400

2DE = two-dimensional echocardiography; RT3DE = real time three-dimensional echocardiography; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; SDI = systolic dyssynchrony index.

4 | DISCUSSION

Left bundle branch block (LBBB) is an interruption in the normal electrical sequence of activation of the heart muscle. This is reflected by an abnormal pattern seen on the surface electrocardiogram (ECG). This block may occur along the left bundle branch arising from the His-Purkinje system and may result in various ECG patterns, it may be rarely seen in asymptomatic young individuals with a structurally normal heart, but it is often associated with underlying heart diseaseespeciallywhenitisofrecentonset***Scherbaketal.2020***[10]

Theaimofthisstudywastoevaluatetheroleofdys-synchronyindex(SDI)-which is thestandard deviation (SD) of the time to reach minimum regionalvolume for each segment- in assessment of LVEF and left ventricular volumesaccurately in patients with LBBB and this parameter can be easily measured byRT3DE.

Van Dijk et al 2008 [11]showed in an asymptomatic cohort study that patientswith LBBB had lower LVEF compared to individuals without LBBB by usingRT3DE.Theyalsofoundanegativecorrelationbetweenthemagnitudeofdyssynchrony and LVEF. This finding indicates the importance of the term called"dyssynchrony" as a determinant of LV function which was referred as "systolicdyssynchronyindex" (SDI)

Ali K. Cabuk et al.2018 [12]concluded that it might be reasonable to assessLV function by RT3DE rather than 2DE in LBBB population as the measuredLVEF was lower and systolic volumes were higher with RT3DE compared to 2DEin patients with high SDI. This finding was recognized both in participants withnormalandreducedejectionfraction.

In the light of previous studies as ***Van Dijk et al 2008***[11]and ***Ali K. Cabuk et al.2018***[12] . Which accepted SDI as equal or higher than 6.5 and 6 respectively as high SDI ; we accepted SDI as equal or higher than 7 as high SDI .

Ourstudyincluded65patients,26femalesrepresented40%and39males

represented 60% with their mean of age 54.97 ± 13.83 with the range 32 to 80years. It showed that there was highly statistically significant difference foundbetween 2DE and RT3DE regarding LVESVI and LVEF in the group with highSDI (more than or equal 7), while there was no statistical significant differencefound between 2DE and RT3DEregarding LVEDVI, LVESVI and LVEF in thegroup with lesser SDI (less than 7). One can assume thatdyssynchrony might bethecausalfactorforincorrecttiminginendocardialborderdetectionin2DEassessment. We can speculate the importance of border definition, editing frame byframe,withQlabsoftware aftersequence analysiswhichisimpossiblewith2DE.

Not surprisingly, duration of QRS complex was positively correlated withSDI, and both of them are good discriminators of responders and nonresponders toCRT. It's known that patients with advanced heart failure and LBBB benefits fromresynchronizationtherapy intermsof quality of lifeandsurvey.

Xiao et al 1999 [13]reported association of LBBB with deterioration of LVsystolic function in patients with cardiomyopathy. Also, this association has beenquantified by ***Zhou et al 2000*** [14]who showed that the LBBB-dependent activationabnormalities had a dominant effect on the deterioration of LV function. Moreover,***Brunekreeft et al 2007*** [15]confirmed a significant difference in left ventricularvolumes,andLVEF betweentwo groupswithandwithoutLBBB.

Witt et al 2016 [16] showed in their study that patients with mild to moderatereducedLVEF(36%–50%)andLBBBhadpooreroutcomesthanthosewithout conduction disturbance, and they indicated LBBB as an independent predictor ofmortality.

The kind of regional wall motion abnormalites caused by dyssynchronizedcontractionofLVinpopulationwithLBBBseemstoleadtoalessreliablemeasurement of LVEF by 2DE ***Risum et al., 2015*** [17]. ***Vernooy et al 2005*** [18]showed increased mechanical dyssynchrony in asymptomatic LBBB patients andthe significant increased mechanical dyssynchrony in symptomatic LBBB patientsintheirstudy,mightbeheldresponsiblefortheobservedmildglobalLVdysfunction in asymptomatic LBBB patients and severe global LV dysfunction insymptomatic LBBB patients with similar QRS durations and co-morbidity. Thus,theydemonstratedthatmechanicaldyssynchronymightnegativelyaffectLVfunctionandthe resultingsymptomatic status.

In our studied cases diastolic volumes were similar between two modalities,butsystolic volumes were underestimated by 2DE. As, LBBB has an impact onventricular systole not on diastole, the pronounced difference in systolic phaseseemstobe logical.

Our findings suggest that if we would evaluate LV systolic function by only2DE and decide the treatment strategy, we would have probably misdiagnosed aproportion of patients as their LVEF > 35% while in fact their ejection fractionmightbeunder35%becauseofhighSDI.Thisis,ofcourse,notastrongrecommendation because of small sample size which is one of the limitations ofthisstudy,butitmaypavethewayforfurtherstudieswithlargercohortsaddressing to this particular population who have borderline LVEF (ie, between35% and 50%). We did not perform cardiac magnetic resonance (CMR), the goldstandardmethod,toassessLVEFasareferencemethod.Thismightbeanother limitation of our study; however, the compatibility of RT3DE with CMR wasshowninformertrialsandmeta-analysis***Milleretal., 2012***[19]

Wood et al.,2014 [20], stated that it is essential to evaluate cardiac functionaccurately in this particular population not to deprive them of this therapeuticoption **;** As in LBBB or right ventricular pacing-induced LBBB were found to beassociatedwithfuturedevelopmentofheartfailureandhighermortality.

In contrast to other published single- center studies, ***Driessen*****et al. 2014** [21]speculated that RT3DE underestimates LV volumes compared to CMR with mostoflessexperiencedoperators.***Solimanetal2008***[22]alsoreportedthesameunderestimation of LV volumes in a comparative study between RT3DE and CMRin daily practice but only in patient with good acoustic window that RT3DEwascompatiblewithCMR.

Mor-Avi et al 2008 [23]in multi-center study for validation of RT3DE incomparisonwithCMR concludedthatThe RT3DE-derivedLV volumeswereunderestimatedinmostpatientsbecauseRT3DEimagingcannotdifferentiatebetweenthe myocardiumandtrabeculae.

Nevertheless, they aimed to be representative of clinical practice and enrolledpatients in an unselected fashion. We excluded all patients with poor image qualityandeliminatedtheimpactofinadequate imagingonourresults.

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