

Evaluation of Ejection Fraction in Patients with Cardiac Resynchronization Therapy by Two and Three Dimensional Echocardiography

Anil OM

Department of cardiology, Manmohan Cardiothoracic Vascular and Transplant Centre, Maharajgunj, Kathmandu, Nepal

Corresponding Author: Dr Om Murti Anil,

E-mail: drommurti@yahoo.com

Abstract

Introduction: Since assessment of left ventricular ejection fraction (LVEF) is crucial for evaluation of patients with cardiac resynchronization therapy (CRT) device both for selection of potential candidates for CRT as well as assessing outcome of therapy, we compared LVEF in patients with CRT device by two dimensional and three dimensional echocardiography.

Methods: Two dimensional echocardiography (2DE) was performed first with CRT device on. LVEF obtained by modified biplane Simpson's Rule. Then real time three dimensional echocardiography (3DE) was performed by (iE 33, PHILIPS Machine). Procedure was repeated with CRT device off.

Results: A total of 19 patients aged 54.6 ± 11.2 years (Range: 32 years to 75 years) were studied. LVEF measured by 2DE and 3DE, with CRT device off, was $22 \pm 4\%$ (17-27%) and $24 \pm 3\%$ (15-27%) respectively. With CRT device on, LVEF measured by 2DE and 3DE was $26.6 \pm 4.1\%$ (22-32%) and $31.3 \pm 5.8\%$ (25-41%) respectively.

Conclusion: Two dimensional echocardiography underestimates LVEF as compared to three dimensional echocardiography. Cardiac resynchronization therapy (CRT) improves LVEF measured either by two or three dimensional echocardiography.

Keywords: Dilated cardiomyopathy, Echocardiography, Cardiac Resynchronization Therapy.

Introduction

Dilated cardiomyopathy (DCM) is a myocardial disorder characterized by a dilated left ventricular chamber and systolic dysfunction. DCM commonly results in congestive heart failure (CHF) and is the most common form of cardiomyopathy and reason for cardiac transplantation in adults and children.¹

Until recently, lifestyle changes, drugs and, sometimes, surgery were the only treatment options. At present, cardiac resynchronization therapy (CRT) is considered an important step forward in the treatment of patients with severe heart failure. Till date, several large randomized trials have shown the sustained beneficial effects of CRT on heart failure symptoms and left ventricular (LV) function.²⁻⁴

For evaluation of potential candidates to CRT, assessment of LV ejection fraction (EF) is crucial and, after implantation, quantification of LV end-systolic volume (LVESV) along with ejection fraction is probably the most clinical meaningful marker of therapy success. LV volume and EF from linear dimensions from 2D images using the methods of Teichholz or Quinones may be inaccurate because they are based on geometric assumptions.^{5,6} The most commonly used method for volume measurement recommended by the American Society of Echocardiography is the biplane method of disks (modified Simpson's rule).⁷

However, 2D methods still have technical limitations for LV volume measurement in patients with LV asynergy, especially with LV distortion. Underestimation of LV



volume has been reported compared with angiography or magnetic resonance imaging (MRI).⁸⁻¹¹ Errors in image plane positioning may be the most important problem in 2D echocardiography for the LV volume estimation. The apex is frequently foreshortened in the apical views because of difficulty in obtaining an adequate apical echocardiography window in most patients.⁶ The biplane modified Simpson's rule is recommended but this also has significant limitations, relying on good endocardial border definition which may be suboptimal in up to 15% of patients.¹² The use of contrast agents has been shown to overcome this problem in the majority of patients. The technique is highly operator dependent with a standard deviation of 8.5% around the mean EF.¹³ Three dimensional (3D) echocardiography has been shown to improve the reproducibility of LV volume calculation and EF with similar accuracy to MRI.¹⁴

The development of Real time three dimensional echocardiography (RT-3DE) has made the echocardiographic approach more feasible and indicate that RT-3DE is a feasible approach to reduce test-retest variation and improve accuracy of LV volume, EF, and mass measurements in follow-up LV assessment in daily practice. The value of RT3DE imaging in this context has been demonstrated by multiple studies that compared RT3DE volume measurements with widely accepted reference techniques, including radionuclide ventriculography and cardiac magnetic resonance (CMR).¹⁵⁻¹⁶

Real time three dimensional echocardiography (RT3DE) has been found to be more accurate than two dimensional (2D) echocardiography to quantify LV volumes and ejection fraction. Therefore, real time three dimensional echocardiography (RT3DE) may be the method of choice for an accurate estimate of LV volumes and function and hence can be used for selection of candidates for CRT as well as evaluation of outcome after CRT device implantation.

Methodology

Patients with dilated cardiomyopathy with cardiac resynchronization therapy (CRT) device and under follow up in department of cardiology at All India Institute of Medical Sciences (AIIMS) were enrolled in this study. All enrolled patients underwent two dimensional echocardiography first with CRT device on. Left ventricle dimensions were first measured by M Mode echocardiography. This was followed by measurement of end diastolic volume; end systolic volume and ejection fraction by biplane Simpson's rule. Three dimensional echocardiography by real time full volume method was then conducted. In this method one cycle of 4 beats was recorded with held respiration.

Apical four chamber view was used for above measurement. Endocardial border was traced manually. Acquired real time image was subsequently analyzed. This examination protocol was conducted again exactly in same way with CRT device off. All patients were assessed for hemodynamic stability and pacemaker dependency before CRT was switched off and echocardiography examination (both two and three dimensional echocardiography) was then completed as described above. Patient was carefully observed during this examination period particularly when CRT device was off. CRT was then switched on after completion of test.

Statistical analysis: Continuous variables are expressed as mean value \pm standard deviation (SD). Besides descriptive statistics, nonparametric wilcoxon signed ranks test (wherever applicable) was applied to compare between two groups for each parameters. The significance was observed if p value was < 0.05 . SPSS software (15.0 version, SPSS Inc) was used for statistical analysis.

Results

Nineteen adult patients (12 male, 7 female) were included in this study. Mean age at the time of enrolment was 54.6 ± 11.2 years (Range: 32 years to 75 years); Most of patients were < 60 years of age (14/19, 73.7%). Only three patients were more than 70 years of age. Mean duration of symptoms at the time of enrolment into study was 3 years (6 months to 6 years).

Fifteen cases were in NYHA class III (79%) and four cases (21%) in Class IV (ambulatory) at the time of implantation. Four patients had history of hospitalization within 1 year of implantation. They were medically stabilized before receiving CRT. At the time of implantation of CRT device, all patients were hemodynamically stable and under maximal medical therapy. All patients had expected survival of more than one year at the time of implantation. Five patients had history of hemodynamically significant VT and they underwent CRT-D (CRT + ICD) implantation.

Left bundle branch block was present in 13/19 (68%) of cases. Right bundle branch block was present in 2/16 cases (1%). In four cases nonspecific intraventricular conduction defect was present. Mean QRS duration was 160 ± 18 ms. Seven patients had some degree of mitral regurgitation. Out of these four had mild MR and three had moderate MR. Valves were found to be structurally normal in all cases.

As standard treatment, loop diuretics were prescribed in all nineteen cases. Furosemide in 13 cases and torsemide in six cases. Spironolactone was used in 10 cases (52.6%). Lanoxin was used in 17 cases (89.5%). Angiotensin



converting enzyme inhibitors (ACEI) were used in 14 (74%) cases. Carvedilol was used in 11 cases (58%).

A) Echocardiographic parameters when CRT device was off

1) Dimensions by M Mode : Mean Aortic diameter was 23.5 ±1.6 mm (21-27mm). Mean LA diameter was 40 ± 2.6mm (37-45mm). Similarly mean IVS and posterior wall thickness were 9.7±0.7mm (9-11mm) and 9.8±0.8 mm (9-11mm). Mean LV end systolic diameter was 59±5mm (53-72mm). And mean LV end diastolic diameter was 67 ± 5.5mm (61-82mm). Table 1

Table 1 Dimensions measured on M mode

| Parameter | Mean ±SD(range) CRT device off (mm) | Mean ±SD(range) CRT device on (mm) | P value |
|---------------------------------|--|---------------------------------------|---------|
| Aorta | 23.5±1.6(21-27) | 23.51(22-26) | 0.82 |
| Left atrium (LA) | 40.7±2.6(37-45) | 38±3(32-42) | 0.001 |
| IVS thickness | 9.7±0.7(9-11) | 10±0.68(9-11) | 0.33 |
| Posterior wall thickness | 9.8± 0.7(9-11) | 9.8±0.8(9-11) | 0.79 |
| LVESD | 59±5 (53-72) | 57±4.7(51-69) | 0.007 |
| LVEDD | 67 ±5.5 (61-82) | 66±5.8(59-82) | 0.016 |

Interventricular septum (IVS) LV end systolic dimension (LVESD) LV end diastolic dimension (LVEDD)

2) LV volume : LV volume was first calculated by Simpson's method in apical 4 chamber view and apical 2 chamber view. Mean LV end systolic volume in apical four chamber (A4C) view, apical two chamber (A2C) view and biplane method was 165±46ml (121-253ml); 151±43ml (96-225 ml) and 159 ± 44ml (113-243ml) respectively. Similarly Mean LV end diastolic volume in apical four chamber view, two chamber view and biplane method was 216±52ml (165-308ml), 193±53ml (134-278ml) and 214±50ml (162-293ml) respectively. Table 2

Table 2 Left Ventricle volume and ejection fraction

| Parameter | Mean ±SD(range) With CRT device off | Mean ±SD(range) With CRT device on | P value |
|------------------|--|---------------------------------------|---------|
| LVESV A4C | 165±46 (121-253) | 154±39(115-226) | 0.0001 |
| LVESV A2C | 151±43(96-225) | 139±40(89-211) | 0.0001 |
| LVEDV A4C | 216±52(165-308) | 205±49(152-284) | 0.0001 |
| LVEDV A2C | 193±53(134-278) | 183±47(125-254) | 0.001 |
| LVESV BP | 159±44(113-243) | 147±40(104-208) | 0.001 |
| LVEDV BP | 214±50(162-293) | 206±47(156-288) | 0.0001 |
| LVESV 3D | 174±50(121-280) | 155±38(112-218) | 0.001 |
| LVEDV 3D | 234±61(174-330) | 217±47(171-296) | 0.001 |
| LVEF A4C | 21.5±2.5 % (18-24%) | 25.5±2 % (23-28%) | 0.0001 |
| LVEF A2C | 23±2.6 % (19-28%) | 26±2.6% (24-32%) | 0.002 |
| LVEF BP | 22±4%(17-27%) | 26.6±4.1 % (22-32%) | 0.0001 |
| LVEF 3D | 24 ±3% (15-27%) | 31.3±5.8 % (25-41%) | 0.0001 |

LVEF = left ventricle ejection fraction, LVEDV= left ventricle end diastolic volume, LVESV = left ventricle end systolic volume, A4C = apical four chamber view, A2C= apical two chamber view, BP = biplane method, 3D = three dimensional.

3) Ejection fraction by two dimensional echocardiography : LV ejection fraction calculated by Simpson's method. Both apical four chamber view and two chamber views were used. LV ejection fraction in apical four chamber view, two chamber view and biplane method was 21.5±2.5% (18-24%), 23±2.6 % (19-28%) and 22±4 % (17-27%) respectively.

4) Three dimensional echocardiography : Mean LV end systolic volume by three dimensional methods was 174±50 ml (121-280ml). Mean LV end diastolic volume was 234±61 ml (174-330ml). Mean LV ejection fraction by real time 3DE before CRT was 24 ±3% (15-27%).



Table 3. LV volume with CRT device off

| LV parameter | 2DE (biplane) | 3DE | P value |
|--------------|-----------------|-----------------|---------|
| LVESV | 159±44(113-243) | 174±50(121-280) | 0.0001 |
| LVEDV | 214±50(162-293) | 234±61(174-330) | 0.0001 |
| LVEF | 22±4 % (17-27%) | 24 ±3% (15-27%) | 0.001 |

B) Clinical and echocardiographic response with CRT device on

In three out of 10 cases there was subjective improvement in symptoms at 48 hrs of implantation. Mean QRS duration after CRT was 143 ± 22 ms. In three cases severity of mitral regurgitation had decreased. Mean Aortic diameter was 23.51mm (22-26mm). Mean LA diameter was 38±3mm (32-42mm). Mean IVS and posterior wall thickness was 10±0.68mm (9-11mm) and 9.8±0.8mm (9-11mm) respectively. Mean LV end systolic and end diastolic volume was 57±4.7mm (51-69mm) and 57±4.7mm (51-69mm) respectively.

Mean LV end systolic volume in apical four chamber view, two chamber view and biplane method, with CRT device on, was 154±39 ml(115-226ml), 139±40ml(89-211ml) and 147±40ml (104-208ml) respectively. Similarly mean LV end diastolic volume in apical four chamber view, two chamber view and biplane method was 205±49ml (152-284ml), 183±47ml (125-254ml) and 206±47ml (156-288ml) respectively. Table 4

Table 4 LV volume with CRT device on

| LV parameter | 2DE (biplane) | 3DE | P value |
|--------------|---------------------|-------------------|---------|
| LVESV | 147±40(104-208) | 155±38(112-218) | 0.0001 |
| LVEDV | 206±47(156-288) | 217±47(171-296) | 0.0001 |
| LVEF | 26.6±4.1 % (22-32%) | 31.3±5.8%(25-41%) | 0.0001 |

LVEF in apical four chamber view, two chamber view and biplane method with CRT device on, was 25.5±2 % (23-28%), 26±2.6 % (24-32%) and 26.6±4.1 % (22-

32%) respectively. Mean LV end systolic volume and end diastolic volume by three dimensional method was 155±38ml (112-218ml) and 217±47ml (171-296ml) respectively. Mean LV ejection fraction by real time three dimensional echocardiography was 31.3±5.8% (25-41%). Table 4

Discussion

Mean age of participants in our study was 54.6 ±11.2 years. There were 63% male participants. Majority of participants were in NYHA class III (79%). LBBB was seen in 68%. Mean duration of symptoms at the time of CRT therapy was 3 years. All these baseline characteristics were comparable to findings of large clinical CRT trials.¹⁷⁻²⁰

As a part of standard treatment, Loop diuretics were used in 100% cases; Spironolactone in 52.6%, Lanoxin in 89.5%, ACE inhibitors 74% and Carvedilol was used in 58.5%. Previous clinical trials also showed similar use of these drugs. Mean LVEF, with CRT device off, in our study was 22 ± 4% (17-27%) by 2DE biplane method. Median LVEF in CARE-HF¹⁷ was 25%, while in MIRACLE ICD¹⁸, mean LVEF was 23.9%. Mean LVEF in COMPANION¹⁹ trial was 20% in CRT-P and 22% in CRT-D group. Mean LVEF in PROSPECT trial²⁰ was 23.6±6 %. Mean LVESV and LVEDV measured by 2DE, with CRT device off, in our study were 147±40ml (104-208ml) and 206± 47ml (156-288ml) respectively and this was comparable to volumes measured by 2DE in other study. In CARE HF study mean LVESV and LVEDV were 168±89 ml and 230 ± 99ml.

LA dimension was significantly higher when measurement done with CRT device off. With CRT device on dimension was 38±3mm (32-42mm) and with CRT device off 40.7±2.6mm (37-45mm) (P value 0.001). There was also significant difference in LV end systolic diameter and LV end diastolic diameters with CRT device on and off. However mean aortic diameter, IVS and PW thickness didn't show significant change with CRT device off or on.

LVESV measured by 2DE and 3DE with CRT device off were 159 ml and 174 ml respectively. With CRT device on, LVESV by 2DE and 3DE was 147 ml and 155 ml. There was 7.54% fall in LVESV when CRT device was on as compared to device off. which is less than 15% value, an echocardiographic marker of success of CRT at six month by 2D method. When we compare the reduction in LVESV with CRT by 3DE method, then reduction in LVESV is slightly higher (10.9%). Failure to achieve the cut off value of 15% reduction in LVESV with CRT was due to measurement of immediate outcome with CRT. (Table 3&4)



When CRT device was off, 2DE measurement underestimated LVESV by 8.6 % ($p = 0.0001$) as compared to 3 DE measurement. Similarly, when CRT device was on, 2DE measurement underestimated LVESV by 5.1 % ($p = 0.0001$) as compared to 3 DE measurement. (Table 3,4). LVEDV measured by 2DE and 3DE with CRT device on was 214 ml and 234 ml respectively. 2DE method clearly underestimated LVEDV measured with CRT device off by 8.5% ($P = 0.0001$). Similarly with CRT device on, 2DE underestimated LVEDV by 5.1% ($p=0.0001$) as compared to 3DE.

LVEF measured by 2DE and 3DE, with CRT device off, was $22 \pm 4\%$ (17-27%) and $24 \pm 3\%$ (15-27%) respectively. It shows that 2DE underestimated LVEF by absolute value of 2% ($p=0.001$). With CRT device on, LVEF measured by 2DE and 3DE was $26.6 \pm 4.1\%$ (22-32%) and $31.3 \pm 5.8\%$ (25-41%) respectively. This clearly showed that there was increase in LVEF after CRT in both methods and it is statistically significant. But compared to 3DE method; 2DE measurement clearly underestimated the LVEF by absolute value 2% when CRT device was off ($p=0.001$) and by absolute value of 4.7% with CRT device on. ($P=0.0001$)

In a case report by Marcelo et al²¹ used real time three dimensional echocardiography to measure LV volume and ejection fraction. LV end-diastolic volume measured by three dimensional echocardiography fell by 3.4% after CRT. LVEDV before and after CRT 166.8ml and 161.2 ml respectively. LV end systolic volume fell by 3.7% after CRT. LVESV before and after CRT were 113.3ml and 109.1 ml respectively. LVEF increased by absolute value of 4.9% after CRT from 27.2% to 32.3%. LVEF before CRT by 2DE was 25%. All above measurements were done at 48 hrs after implantation. Change in LVESV, LVEDV and LVEF after CRT in above report is similar to result in our study.

Conclusion

Cardiac resynchronization therapy improves left ventricular ejection fraction measured either by two dimensional echocardiography or three dimensional echocardiography method. Two dimensional echocardiography underestimates left ventricular ejection fraction as compared to three dimensional echocardiography method. Two dimensional echocardiography also underestimates left ventricular end systolic volume as well as left ventricular end diastolic volume as compared to three dimensional echocardiography method.

Acknowledgment

I owe a special thanks to Dr. R. Yadav, Department of Cardiology, AIIMS New Delhi, for his guidance, support and constructive feedback during echocardiographic

assessment of enrolled cases. I am extremely grateful to Mr Ahuza, department of Biostatistics, who spared no effort in the statistical analysis of this research. I also like to thank all the staffs of echo lab, who helped during data collection.

Conflict of interest: None declared.

References

1. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. *Circulation* 1996; 93: 841–42.
2. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845–53.
3. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; 350:2140–50.
4. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003; 107:1985–90.
5. Quinones MA, Waggoner AD, Reduto LA et al. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. *Circulation* 1981; 64: 744–53.
6. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic–angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 1976; 37: 7–11.
7. Lang RM, Bierig M, Devereux RB et al. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. *J Am Society Echocardiography* 2005; 18: 1440–63.
8. Erbel R, Schweizer P, Lambertz H et al. Echocardiography – a simultaneous analysis of two-dimensional echocardiography and cineventriculography. *Circulation* 1983; 67: 205–15.
9. Starling MR, Crawford MH, Sorensen SG et al. Comparative accuracy of apical biplane cross-sectional echocardiography and gated equilibrium radionuclide



- angiography for estimating left ventricular size and performance. *Circulation* 1981; 63: 1075–84.
10. Folland ED, Parisi AF, Moynihan PF et al. Assessment of left ventricular ejection fraction and volumes by real-time, two-dimensional echocardiography. A comparison of cineangiographic and radionuclide techniques. *Circulation* 1979; 60: 760–6.
 11. Schnittger I, Fitzgerald PJ, Daughters GT et al. Limitations of comparing left ventricular volumes by two dimensional echocardiography, myocardial markers and cineangiography. *Am J Cardiol* 1982; 50: 512–19.
 12. Olszewski R, Timperley J, Cezary S, et al. The clinical applications of contrast echocardiography. *Eur J Echocardiogr* 2007;8:S13–23.
 13. Otterstad JE, Froeland G, St John Sutton M, Holme I. Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. *Eur Heart J* 1997; 18:507–13.
 14. Jenkins C, Bricknell K, Hanekom L, Marwick TH. Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. *J Am Coll Cardiol.* 2004;44:878–86.
 15. Jenkins C, Bricknell K, Hanekom L, Marwick TH. Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. *J Am Coll Cardiol.* 2004;44:878–886.
 16. Nikitin NP, Constantin C, Loh PH, et al. New generation 3-dimensional echocardiography for left ventricular volumetric and functional measurements: comparison with cardiac magnetic resonance. *Eur J Echocardiogr.* 2006; 7:365–372.
 17. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, for the Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* 2005;352:1539–1549.
 18. Young JB, Abraham WT, Smith AL, et al. Multicenter In Sync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA.* 2003;289:2685–2694.
 19. Bristow MR, Saxon LA, Boehmer J, et al. COMPANION Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004;350:2140–2150.
 20. Eugene S. Chung, Angel R. Leon, Luigi Tavazzi, Jing-Ping Sun et al, Results of the Predictors of Response to CRT (PROSPECT) Trial. *Circulation.* 2008;117: 2608-2616.
 21. Marcelo Luiz Campos Vieira, Prasad V. Maddukuri, Robert S. Phang et al, Mechanism of cardiac resynchronization therapy by real time three dimensional echocardiography in patients with heart failure, *Arquivos Brasileiros de Cardiologia - Volume 85, No 5, November 2005.*

