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Original Article

Heart rate manipulation in dilated cardiomyopathy: Assessing the role of Ivabradine

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ABSTRACT

Background: Heart rate (HR) reduction is of benefit in chronic heart failure (HF). The effect of heart rate reduction using Ivabradine on various echocardiographic parameters in dilated cardiomyopathy has been less investigated.

Methods: Of 187 patients with HF (DCM, NYHA II–IV, baseline HR > 70/min), 125 patients were randomized to standard therapy (beta blockers, ACEI, diuretics, n = 62) or add-on Ivabradine (titrated to maximum 7.5 mg BD, n = 63). Beta-blockers were titrated in both the groups.

Results: At 3 months both groups had improvement in NYHA class, 6 min walk test, Minnesota Living With Heart Failure (MLWHF) scores and fall in BNP, however the magnitude of change was greater in Ivabradine group. Those on Ivabradine also had lower LV volumes, higher LVEF (28.8 ± 3.6 vs 27.2 ± 0.5, p = 0.01) and more favorable LV global strain (11 ± 1.7vs 12.2 ± 1.1, p = <0.001), MPI (0.72 ± 0.1 vs 0.6 ± 0.1, p = <0.001), LV mass (115.2 ± 30 vs 131.4 ± 35, p = 0.007), LV wall stress (219.8 ± 46 vs 238 ± 54) and calculated LV work (366 ± 101 vs 401 ± 102, p = 0.05). The benefit of Ivabradine was sustained at 6 months follow up. The % change in HR was significantly higher in Ivabradine group (−32.2% vs −19.3%, p = 0.001) with no difference in blood pressure. Resting HR < 70/min was achieved in 96.8% vs 27.9%, respectively in the two groups.

Conclusion: Addition of Ivabradine to standard therapy in patients with DCM and symptomatic HF and targeting a heart rate < 70/min improves symptoms, quality of life and various echocardiographic parameters.

1. Introduction

Studies have indicated that lowering heart rate (HR) can help reduce mortality and cardiovascular events by improving the left ventricular filling and favorably affecting the imbalance between myocardial oxygen supply and demand in patients with heart failure (HF).[1–3] Some patients with HF continue to have persistently high HR despite treatment with beta blockers and conventional treatment.[4]

Ivabradine, a novel HR lowering agent, is a selective and specific inhibitor of the "funny" I_f current at concentrations that do not affect other cardiac ionic currents resulting in lack of hemodynamic effects such as reduction of blood pressure, cardiac contractility or atrioventricular conduction, which is often a limitation with beta blockers.[5,6] Improvement in remodeling of the extracellular matrix has also been reported with Ivabradine in animal and experimental models of HF.[7] Despite its benefit being demonstrated in patients with CAD and LV dysfunction,[8,9] the use of Ivabradine in isolated non ischemic HF has been less studied and only a few studies have reported its use in HF secondary to DCM.[10,11]

This prospective randomized study sought to assess whether addition of Ivabradine to conventional treatment while targeting a heart rate reduction of <70/min would improve functional class, exercise tolerance, and left ventricular function in patients with HF secondary to non ischemic dilated cardiomyopathy.

2. Materials and methods

2.1. End points

The primary end point of the study was to assess the superiority of add-on Ivabradine over conventional medical management on the improvement in various echocardiographic parameters. The

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secondary end point was to assess the superiority of add-on Ivabradine over conventional medical management on heart rate and quality-of-life (QOL-NYHA class, 6 min walk test, MLWHF score, BNP levels) parameters.

2.2. Inclusion and exclusion criteria

The study was conducted at the Department of Cardiology at our institution from January 2014 to July 2015 and conformed to the institutional ethical guidelines. Patients with symptomatic HF secondary to idiopathic DCM, NYHA symptomatic class II–IV and LV ejection fraction (LVEF) $\leq$40% and resting HR $>$ 70/min were enrolled after obtaining informed consent. Prior to randomization, all patients were on medical therapy (including beta blocker, angiotensin converting enzyme inhibitors, diuretics and digoxin) for at least 12 weeks prior to enrolment into the study. Patients with atrial fibrillation, baseline bundle branch blocks, deranged renal functions (serum creatinine $>$3 mg/dl), deranged liver functions, significant valvular heart disease, known coronary artery disease (by means of history or prior coronary angiogram), malignancy and inability to provide consent were excluded from the study.

2.3. Randomization, drug titration

Patients were randomized in the sequence of 1:1 by computerized random number generation protocol to either guideline directed optimal medical therapy: (control group)[4] or optimal medical therapy with add-on Ivabradine (Ivabradine group). Ivabradine was initiated in the dose of 2.5 mg bd. Both beta blockers and Ivabradine were up-titrated over next 2–4 weeks (carvedilol and metoprolol were titrated, if tolerated to a maximum dose of 50 or 200 mg, respectively, while Ivabradine to 7.5 mg twice daily). The up-titration was guided by the patients' HR and the target dose was not the maximum dose mentioned, but the maximally tolerated dose that produced a resting HR $<$ 70/min. The drug dose was reduced or withdrawn (if needed) in case of intolerance, symptomatic bradycardia (in case of either beta blocker or Ivabradine) or visual disturbances (in case of Ivabradine).

2.4. Data collection

Baseline assessment of symptomatic class was done using the NYHA classification while functional exercise capacity was estimated using the 6 min walk test. The Minnesota Living With Heart Failure questionnaire (MLWHF) was used to assess the quality of life.[12] All patients underwent baseline investigations including complete hemogram, renal and liver functions, blood sugar, serum electrolytes and BNP levels. Levels of BNP were assessed using fluorescence immunoassay with a commercially available kit (Alere Triage Cardio 3 Panel, Alere, Inc., San Diego, CA, USA). All parameters were re-assessed at a follow up of 3 and 6 months.

2.5. Echocardiography

Detailed echocardiography was performed using a GE Vivid 7 ECHO machine (GE Healthcare, Waukesha, WI) by an operator who was blinded to the clinical data. Various 2D Echocardiographic and Doppler indices, including left ventricular end-diastolic dimensions and volumes (LVEDD, LVEDV), left ventricular end-systolic dimensions and volumes (LVESD, LVESV) and LVEF were recorded. The LV dimensions were obtained from M mode parasternal long-axis views while LV volumes were obtained from the apical four- and two-chamber views. Using the modified Simpson's rule, ejection fraction was automatically calculated as the difference between end-diastolic volume and end-systolic volume normalized to end-diastolic volume. Mean LV wall stress (mmHg) was calculated as $(SAP \times (EDD + ESD)/2 \times PWTd + PWTs)$, corrected LV mass (g) as $0.8\{1.04[([LVEDD + IVSd + PWd]^3 - LVEDD^3)]\} + 0.6$ and LV work (mmHg.L/mt) as SV X HR X ESBP (SAP-systolic arterial pressure, EDD-end diastolic dimension, ESD-end systolic dimension, PWTd and PWTs-posterior wall thickness in diastole and systole respectively, IVS-interventricular septum, SV-stroke volume and ESBP-end systolic blood pressure).[13,14]

Transmitral flow velocities (peak early: E wave and late: A wave), their ratio (E/A); velocity time integral (EVTI and A VTI), their ratio (E/A VTI), E deceleration time and tissue Doppler indices (TDI E/e'septal and E/e' lateral) were also recorded in all patients. Tei index or Myocardial Performance Index (MPI), an echocardiographic Doppler load independent index of combined systolic and diastolic function, was calculated as isovolumic relaxation time plus isovolumic contraction time divided by ejection time. Global LV longitudinal strain was also assessed by TDI imaging. Apical 4 chamber view was used to record the cardiac cycle in TDI mode at a frame rate of more than 100 per second, following which 2 mm volume samples were placed at 6 different segments of LV in apical 4 chamber view for strain analysis. The average of these 6 segments resulted in the global longitudinal strain values expressed in '$-$%' representing the fractional contraction percentage of the reference segment. All patients underwent repeat echocardiographic assessment at 3 and 6 months of follow up.

2.6. Statistical analysis

Continuous variables are presented as means $\pm$ standard deviation (SD) and categorical variables as percentages. Statistical analysis was performed using commercially available software (SPSS Version 17.0, Texas). Paired continuous variables were compared using paired *t*-test for normally distributed data. Independent continuous variables were compared using a two-sample *t*-test for normally distributed data. Categorical variables were compared with the use of the Pearson chi-square test. The Pearson correlation coefficient was obtained to examine the linear relationship between heart rate and other continuous variables. p value $<$ 0.05 (2 tailed) was considered statistically significant. Binomial logistic regression analysis was done to derive the univariate and multivariate predictors for ejection fraction $>$30% at the end of follow up. The study conforms to ethical principles in the Declaration of Helsinki and the study has been approved by the local institutional ethics committee.

3. Results

A total of 187 patients were screened of which 62 were excluded (associated CAD in 18, significant valvular heart disease in 19, atrial fibrillation in 14 and poor echo window in 11). Hence 125 patients (mean age 47.2 $\pm$ 15 years, 56.9% males) were included of which 63 were in the control group and 62 in the Ivabradine group. The mean LVEF of the study population was 26.3 $\pm$ 3.6% (range 17.9%–35.2%), mean global LV strain was $-$10.02 $\pm$ 1.5% ($-$6.4 to $-$16.3%) while mean BNP was 750 $\pm$ 442 pg/dl (range 110–2000 pg/dl). Overall, 32.5% had hypertension while 34.1% had diabetes. All patients were on beta blockers and ACE inhibitors while 87%, 67% and 27% were on diuretics, digoxin and spironolactone respectively.

3.1. Comparison of baseline characteristics (Tables 1 and 2)

There was no significant difference between the two groups with respect to baseline demographic, clinical characteristics and medications. Mean LVEF (26.7 $\pm$ 3.6 vs 26 $\pm$ 3.6% (p = 0.3), global LV

Table 1
Comparison of Clinical variables at baseline.

Parameter	Total	Control (62)	Ivabradine (63)	p
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (yrs)	47.2 ± 15	45.4 ± 13.8	48.9 ± 16	0.20
BMI	23.5 ± 2.9	23.3 ± 3.4	23.8 ± 2.9	0.35
Male: Female (%)	56.9/43.1	59/41	55/45	0.70
Hypertension (%)	32.5	32.8	32.3	0.90
Diabetes (%)	34.1	36.1	32.3	0.70
Duration of symptoms (months)	15.3 ± 14.9	15.1 ± 12.6	15.9 ± 17	0.80
NYHA class	3.2 ± 0.6	3.2 ± 0.4	3.3 ± 0.5	0.73
Heart rate	94.9 ± 10	94.6 ± 8.7	95.3 ± 11.04	0.70
Systolic BP	124 ± 14.7	124.3 ± 13.8	124.4 ± 15.6	0.97
Diastolic BP	78.9 ± 10	79.02 ± 8.8	78.9 ± 10.9	0.95
6 min Walk Test (meters)	327 ± 52	333.9 ± 60.1	321.5 ± 42.4	0.20
BNP (pg/ml)	750 ± 442	733.8 ± 429	766.2 ± 458	0.70
MLWHF score	78.2 ± 8	77.9 ± 7.6	78.4 ± 8.4	0.70
Dose of carvedilol in mg	8.3 ± 3.9	8.2 ± 3.4	8.5 ± 4.5	0.70
Dose of metoprolol in mg	35.8 ± 12.5	36.3 ± 12.6	35 ± 12.4	0.70
Dose of enalapril in mg	9.4 ± 4.9	9.4 ± 4.7	9.5 ± 5.2	0.90
Dose of furosemide in mg	30.7 ± 7.7	32.1 ± 7.3	29.5 ± 7.9	0.70
Dose of spironolactone in mg	45 ± 18.2	48.3 ± 18.7	41.5 ± 16.7	0.80
Dose of digoxin in mg	0.24 ± 0.01	0.24 ± 0.02	0.25 ± 0	0.10

BMI-Body Mass Index; BP-blood pressure; BNP-Brain natriuretic peptide; MLWHF-Minnesota Living With Heart Failure Questionnaire.

strain (−9.9 ± 1.7vs−10 ± 1.2%, p = 0.48) and MPI 0.77 ± 0.15 vs 0.77 ± 0.2, p = 0.9) were also not significantly different along with the rest of the recorded echocardiographic parameters.

3.2. Comparison at 3 months follow up

The Ivabradine group had significantly better NYHA class (2.07 ± 0.18 vs 2.5 ± 0.6, p < 0.001), longer 6 min walk test (407 ± 56 vs 350 + 66.8 m, p < 0.001), lower MLWHW scores (58.3 ± 10.2 vs 71.4 ± 11.2, p < 0.001) and lower BNP levels (354 ± 192 vs 590 ± 395 pg/dl, p < 0.001) as compared to the controls. The mean HR was also significantly lower in the Ivabradine arm whilst there was no difference in BP between both the groups (HR = 80.1 ± 6.8 vs 87.3 ± 6.7 p = 0.01; Systolic BP 119 ± 14 vs 111.5 ± 11 mmhg, p = 0.823).

3.2.1. Change in echocardiographic variables at 3 months

Although both groups showed improvement in echocardiographic parameters, those receiving Ivabradine had lower LV systolic and diastolic dimensions and LV volumes as compared to controls. (Table 3) The mean LVEF (27.2 ± 3.5 vs 28.8 ± 3.6, p = 0.017), LV global strain (11 ± 1.7vs 12.2 ± 1.1, p = <0.001) and MPI (072 ± 0.1 vs 0.6 ± 0.1, p = <0.001) were also significantly more favorable in those on Ivabradine. Other parameters like LV mass, LV wall stress, calculated LV work, diastolic echocardiographic parameters (E/A velocity ratio, E/A VTI) and tissue Doppler E/e' ratios in the septal and lateral annulus were also better in the Ivabradine group.

Table 2
Comparison of Echocardiography variables at baseline.

Parameter	Total	Control (62)	Ivabradine (63)	p
	Mean ± SD	Mean ± SD	Mean ± SD	
LVEDD (mm)	6.3 ± 0.5	6.3 ± 0.5	6.3 ± 0.4	0.90
LVESD (mm)	4.9 ± 0.5	4.9 ± 0.5	5 ± 0.5	0.40
LVEDVI (ml/m^2)	113.5 ± 23	112.3 ± 23	114.8 ± 24	0.50
LVESVI (ml/m^2)	83.7 ± 18.3	82.4 ± 18	84.9 ± 18	0.40
LVEF (%)	26.38 ± 3.6	26.7 ± 3.6	26 ± 3.6	0.30
FS (%)	20.56 ± 4.1	21.1 ± 3.7	20 ± 4.3	0.10
MPI	0.77 ± 0.2	0.77 ± 0.15	0.77 ± 0.2	0.90
LV global strain (−%)	10.02 ± 1.5	9.9 ± 1.7	10 ± 1.2	0.48
LV Mass indexed	125.9 ± 34.6	126.6 ± 37	125.3 ± 33	0.80
LV wall mean Stress index	272.5 ± 61.7	274.3 ± 65	270.6 ± 58	0.70
LV work	508 ± 135	502 ± 128	514 ± 143	0.60
E/A velocity	2.2 ± 1.1	2.1 ± 1.1	2.4 ± 1.1	0.30
E/A VTI	2.2 ± 1.05	2.1 ± 1	2.3 ± 1	0.20
E/e' septal	16.9 ± 6.4	17.5 ± 7	16.4 ± 5	0.30
E/e' lateral	14.2 ± 4.5	13.5 ± 5	14.8 ± 4	0.10

LVEDD-left ventricular end-diastolic dimension; LVESD-left ventricular end-systolic dimension; LVESVI-left ventricular end-systolic volume indexed to body surface area; LVEDVI-left ventricular end-diastolic volume indexed to body surface area; LVEF-left ventricular ejection fraction; FS-Fractional shortening; MPI-Myocardial performance index; VTI-Velocity Time Integral.

3.3. Comparison at 6 months follow up

At 6 months, patients receiving Ivabradine as compared to controls had significantly better NYHA class (1.4 ± 0.5 vs 2.1 ± 0.7), longer 6 min walk test (493.5 ± 4.6 vs 367 ± 82 m), lower MLWHW scores (44.5 ± 8 vs 67.3 ± 17) and lower BNP levels (112 ± 58 vs 471 ± 366 pg/dl) (all values of p < 0.001). The mean HR at 6 months was also significantly lower amongst those on Ivabradine (63.8 ± 3.6 vs 75.9 ± 8.4/min, p < 0.001) whilst there was no difference in SBP (113.9 ± 11.5 vs 109.7 ± 10.3 mmhg, p = 0.2).

3.3.1. Change in echocardiographic variables at 6 months

Those receiving Ivabradine had lower LV systolic and diastolic dimensions and indexed LV volumes as compared to those on conventional therapy (Table 3). The mean LVEF (30.1 ± 4% vs 28.1 ± 4%), FS (33.7 ± 7% vs 24.4 ± 5%), LV global strain (−14.4 ± 1.4% vs −11.5 ± 2.2%) and MPI (0.5 ± 0.04 vs 0.7 ± 0.3) were also significantly more favorable in those on Ivabradine (p values < 0.001). Other parameters like LV mass, LV global strain, LV wall stress and calculated LV work were also lower in the Ivabradine group at 6 months. Those receiving Ivabradine, also had more favorable diastolic echocardiographic parameters (E/A velocity ratio, E/A VTI) and Tissue Doppler E/e' ratios in the septal and lateral annulus. From baseline to 6 months, the % changes in LVEF (↑18 ± 7% vs ↑5.3 ± 6%), LV global strain (↑44 ± 24% vs ↑17 ± 23%), LV mass (↓32 ± 16% vs ↑11 ± 20%), LV stress (↓32 ± 10% vs ↓24 ± 14%) and LV work (↓50 ± 9% vs ↓30 ± 10%) were also significantly better (all p values < 0.001) in those on Ivabradine than in the controls.

3.4. Absolute and % changes in heart rate

In those receiving Ivabradine the mean HR per minute reduced from 95.3 ± 11 at the beginning of the study to 63.8 ± 3.6, p < 0.001

Table 3
Comparison of Echocardiography parameters at 3 and 6 months in Control vs Ivabradine arm.

Parameter	3 months			6 months		
	Control	Ivabradine	p	Control	Ivabradine	p
LVEDD (mm)	6.2 ± 0.5	5.9 ± 0.4	0.001	6.1 ± 0.5	5.6 ± 0.4	<0.001
LVESD (mm)	4.8 ± 0.5	4.4 ± 0.4	<0.001	4.6 ± 0.6	3.7 ± 0.4	<0.001
LVEDVI (ml/m^2)	111 ± 24	100.3 ± 18	0.005	107.6 ± 23	87.7 ± 16	<0.001
LVESVI (ml/m^2)	81.2 ± 18	71 ± 13	0.001	77 ± 17	60.6 ± 11	<0.001
LVEF (%)	27.2 ± 3.5	28.8 ± 3.6	0.017	28.1 ± 4	30.1 ± 4	<0.001
LV global strain (−%)	11 ± 1.7	12.2 ± 1.1	<0.001	11.5 ± 2.2	14.4 ± 1.4	<0.001
LV mass index	131.4 ± 35	115.2 ± 30	0.007	138 ± 36	107 ± 27	<0.001
LV wall mean Stress index	238 ± 54	219.8 ± 46	0.04	210 ± 55	183 ± 35	0.002
LV work	402 ± 102	366 ± 101	0.052	348 ± 98	255 ± 70	<0.001
E/A velocity	1.8 ± 0.7	1.4 ± 0.4	<0.001	1.5 ± 0.6	0.9 ± 0.3	<0.001
E/A VTI	1.77 ± 0.7	1.38 ± 0.4	<0.001	1.6 ± 0.6	1.1 ± 0.6	<0.001
MPI	0.72 ± 0.1	0.6 ± 0.1	<0.001	0.7 ± 0.13	0.5 ± 0.04	<0.001
E/e' septal	15.6 ± 3.9	13.1 ± 1.9	<0.001	13.2 ± 3.7	9.7 ± 2	<0.001
E/e' lateral	12.3 ± 2.9	10.8 ± 2	<0.001	12 ± 3.4	8.6 ± 2.2	<0.001

LVEDD-left ventricular end-diastolic dimension; LVESD-left ventricular end-systolic dimension; LVESVI-left ventricular end-systolic volume indexed to body surface area; LVEDVI-left ventricular end-diastolic volume indexed to body surface area; LVEF-left ventricular ejection fraction; FS-Fractional shortening; MPI-Myocardial performance index; VTI-Velocity Time Integral.

at 6 months (percent change of ↓32.2 ± 8.15%) as compared to 94.6 ± 8.7 to 75.9 ± 8.4 beats per minute (percent change of ↓19.3 ± 9.4%) in the controls. The greater % change in HR in the Ivabradine group was achieved without any significant difference in systolic blood pressure in both the groups at the end of 6 months (113.9 ± 7.6 vs 109.7 ± 10.3 vs, p = 0.2). At 6 months, 96.8% patients in the Ivabradine group achieved a HR < 70/min whereas only 27.9% could do so in the conventional treatment group. The maximum targeted dose of carvedilol (50 mg) was achieved in 17.8% (add-on Ivabradine group) vs 14.2% (control group, p = ns). None of the patients in either group were able to achieve the maximum targeted dose of metoprolol i.e. 200 mg. The corresponding % of patients able to achieve at least 50% of the target dose of carvedilol (85% vs 75%, p = ns) and metoprolol (50% vs 51%, respectively) was also comparable.

3.5. Clinical events

The mean achieved dose of Ivabradine was 13.3 ± 2.3 mg. The drug was well tolerated and none of the patients discontinued the drug due to adverse effects. Two patients in the Ivabradine arm had reduction of doses due to reporting of visual symptoms. Overall 2 patients died during follow up (1 each in control and Ivabradine group due to severe lower respiratory tract infection and due to stroke respectively). There were lesser mean number of hospitalizations noted in the Ivabradine group (1.89 ± 0.49 vs 1.66 ± 0.5). There were no reports of new onset atrial fibrillation in those receiving Ivabradine.

3.6. Posthoc analysis on patients with resting HR ≤ 70/min at the end of 6 months

Posthoc analysis on patients with resting HR ≤ 70/min at the end of 6 months (irrespective of the drugs they received) showed that these patients had significantly better NYHA Class (1.4 ± 0.5 vs 2.3 ± 0.6, p < 0.001), longer 6 min walk time (484.9 ± 62 vs 341 ± 53, p < 0.001), better MLWHF score (44 ± 8.4 vs 75 ± 9.4, p < 0.001), lower BNP (104.8 ± 54.9 vs 601 ± 330 pg/dl, p < 0.001) along with higher LVEF (30.4 ± 3.8% vs 27.6 ± 3.6%, p < 0.001) than those with HR > 70/min. (Table 4) These patients also had lower LV dimensions and volumes, lower LV mass, LV stress and LV work and parameters of diastolic function, leading to more favorable values of MPI and global LV strain. All these favorable parameters translated into significantly lesser number of hospitalizations (1.6 ± 0.5 vs 2 ± 0.4, p < 0.001).

Table 4
Comparison of 6 month Echocardiography variables in patients with HR ≤ and >70/mt.

Parameter	HR ≤ 70 (77)	HR > 70 (46)	p
LVEDD (mm)	5.6 ± 0.4	6.2 ± 0.6	<0.001
LVESD (mm)	3.8 ± 0.43	4.8 ± 0.5	<0.001
LVEDVI (ml/m^2)	90.3 ± 17.3	109 ± 24	<0.001
LVESVI (ml/m^2)	63 ± 12.5	79.4 ± 18	<0.001
LVEF (%)	30.4 ± 3.8	27.6 ± 3.6	<0.001
MPI	0.5 ± 0.08	0.7 ± 0.14	<0.001
LV global strain (−%)	14.3 ± 1.4	10.5 ± 1.5	<0.001
SVR	18.2 ± 5.4	14.4 ± 5.3	<0.001
LV Mass indexed	112.8 ± 29.90	138.1 ± 38.5	<0.001
LV wall mean Stress index	180.8 ± 35.3	222.6 ± 55	<0.001
LV work	260.8 ± 66	370 ± 107	<0.001
E/A velocity	1.0 ± 0.6	1.7 ± 0.6	<0.001
E/A VTI	1.1 ± 0.64	1.8 ± 0.67	<0.001
E/e' septal	10.1 ± 2.5	14.6 ± 3.6	<0.001
E/e' lateral	8.8 ± 2.3	12.7 ± 3.4	<0.001
Mean no of Hospitalisations	1.6 ± 0.5	2 ± 0.4	<0.001

LVEDD-left ventricular end-diastolic dimension; LVESD-left ventricular end-systolic dimension; LVESVI-left ventricular end-systolic volume indexed to body surface area; LVEDVI-left ventricular end-diastolic volume indexed to body surface area; LVEF-left ventricular ejection fraction; FS-Fractional shortening; MPI-Myocardial performance index; VTI-Velocity Time Integral; SVR-systemic vascular resistance.

4. Discussion

This study showed that in patients with stable symptomatic HF secondary to DCM, addition of Ivabradine to guideline directed optimal medical therapy resulted in significant improvement in various clinical and echocardiographic variables. At an achieved dose 13.3 ± 2.3 mg (range 10–15 mg/day), Ivabradine was well tolerated and none of the patients demonstrated any drug related adverse effects leading to discontinuation of therapy. As expected, HR reduction was much more robust in those on Ivabradine (a % change of −32.2 ± 8.15%: absolute reduction from 95.3 at baseline to 63.8/min at 6 months) as compared to (−19.3 ± 9.4% in controls: reduction from 94.6 at baseline to 75.9 ± 8.4/min at 6 months). Almost all patients (96.8%) in the Ivabradine group achieved a HR < 70/min as compared to about only one-fourth in the control group. The HR reduction was achieved without any significant difference in SBP between the two groups, reflecting the neutral effects of Ivabradine on BP.

Previous studies assessing the use of Ivabradine in HF have been primarily in those with both ischemic and non ischemic HF[8,9,15–17]

and data in patients with HF secondary to DCM are limited.[10,11] The degree of HR reduction in our study (−19/min with Ivabradine) compared well with what was observed in the SHIFT trial (−15/min)[9] and other studies (−24/min),[10] (−25.9/min),[11] (21.1/min),[15] and (−17.2/min).[16] The % change in EF observed by us (+18 ± 7) was more robust than that reported by Mansour et al.[10] (+6.2 ± 8.3) despite the fact that our patient population was more sick as reflected by the differences in demographics (% in NYHA Class III/IV: 93% vs 81%, mean MLWHF score 78.2 vs 58.8 and baseline LVEF 26.38% vs 32.1% in the two studies. The observed improvement in LVEF from 26 ± 3.6% to 30.1 ± 4% at 6 months by us is also similar to previous reports of beneficial effects of add-on Ivabradine in chronic HF in improving EF (32.3–34.7%),[9,18] 32.1%–34%,[10] 32.6–38.3%[11] and 37.4–41.3%).[16]

In contrast to our report no previous study has assessed the effect of Ivabradine on LV stress, LV mass, LV work, MPI and diastolic echocardiographic parameters. We have assessed and documented improvement in these diverse echocardiographic variables following addition of Ivabradine to optimal medical therapy in chronic symptomatic HF secondary to DCM. The current study also demonstrates improvement in LV strain following use of Ivabradine in chronic HF (% change in LV strain ↑44 ± 24% vs ↑17 ± 23%, $p < 0.001$, in Ivabradine vs controls respectively).

The underlying mechanism for the observed beneficial effects of Ivabradine in chronic HF is postulated to be due to its HR lowering effects. Increasing resting HR in patients with HF serves to maintain cardiac output at the cost of impaired LV filling, increased myocardial O2 consumption, and reduced diastolic duration leading to reduction in coronary perfusion.[19] This translates into better clinical parameters like NYHA class, improved exercise times and quality of life (QOL) scores with lower BNP levels, as observed in our study. Moreover lack of detrimental effects on BP, cardiac output and AV conduction, help it to be synergistically combined with beta blocker and facilitate their up-titration.

Only ~9% of the overall patient population was able to achieve the maximum tolerated dose of beta blocker. The % of patients able to achieve at least 50% of target dose of carvedilol (25 mg) was ~80% while only 50% were able to achieve the target dose (200 mg) of metoprolol. Previous studies have also reported that in HF, only 19–50% of patients could achieve ≥50% of the target daily dose of carvedilol 50 mg.[10,15,17] The mean maximum doses of carvedilol and metoprolol achieved in our study in the Ivabradine and control group were comparable (23.4 ± 12.7 vs 25.4 ± 12.9 mg/day, $p = 0.6$ for carvedilol and 75 ± 31 vs 78.6 ± 24 mg/day, $p = 0.7$ for metoprolol). This compares with the mean achieved dose of carvedilol (37.8 + 13.9 mg/day) in the study by Bagriy et al.[15]

On the other hand, 71.1% patients were able to achieve the targeted maximum Ivabradine dose of 15 mg. Hence in patients with HF (who are especially susceptible to developing drug related adverse effects), those assigned to Ivabradine were more likely to reach target doses than patients receiving carvedilol/metoprolol.

No difference in mortality was noted since only 1 patient died in each group. Although the number of hospitalizations (1.89 ± 0.49 vs 1.66 ± 0.5) were lesser in the Ivabradine group, the numbers were too small to draw a significant comparison. Mansour et al.[10] also reported that over a follow up of 13.5 months, hospitalizations were significantly lesser (1.0 ± 1.4 vs 2.1 ± 1.1, $p = 0.003$) in those on Ivabradine. The SHIFT trial also reported similar findings, with beneficial effects on HF events (death, hospital admissions) within 3 months of initiation of therapy with Ivabradine.[9]

Reduction in HR significantly correlated with better exercise tolerance, MLWHW score, NYHA class, and all parameters of LV systolic and diastolic function and decreased HF hospitalizations. Patients who were able to achieve resting HR ≤ 70/min at 6 months had better NYHA class, longer 6 min walk time and QOL scores than those with higher HR. These patients also had higher LVEF (+3% points greater) and higher LV strain (+4% points greater) than those with HR > 70/min. Although the mean dose of carvedilol (27.8 ± 14.2) and metoprolol (82.7 ± 27.8) was higher in patients with HR ≤ 70/min as compared to those with higher HR (carvedilol 18.7 ± 6.8 mg/day and metoprolol 68 ± 24 mg/day), there was no difference in SBP. Previous meta-analysis of HF trials with beta-blockers have reported a direct association between extent of HR reduction and clinical improvement and survival.[20,21]

The main limitations of our study are that it involved a relatively small number of patients (63 and 62 in each group) and was a single center study, with a short mid-term follow up of 6 months. Multicentre studies with larger number of patients and longer follow up are required to assess mortality benefits, if any, with Ivabradine in these patients. The % of patients who achieved maximally targeted dose of beta blocker was low and most patients could only achieve ~50% of the target dose of beta blocker. Whether, more aggressive beta blocker use and analysis of LV function with techniques other than echocardiography (e.g. Cardiac magnetic resonance imaging) would achieve better results remains speculative. Beta blockers were titrated in both the groups because the design of the study was to assess the added benefits of Ivabradine to an existing guideline based medical management.

5. Conclusion

Our study demonstrates that addition of oral Ivabradine to optimal medical treatment in patients with DCM and symptomatic HF not only improves symptoms, quality of life, BNP levels but also the left ventricular performance as measured by various echocardiographic parameters. The increase in EF following Ivabradine use was accompanied by reduced LV mass, stress and calculated LV work. The observed improvement in various parameters could be secondary to a greater % reduction in HR with Ivabradine than in the controls (−32.2 vs 19.3%).

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Conflicts of interest

The authors have none to declare.

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