

Effect of Race on Left Ventricular Ejection Fraction Decline After Initial Improvement with Beta Blockers in Patients with Non-Ischemic Cardiomyopathy: A Retrospective Analysis

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Abstract

Background Although beta blockers (BBs) are established therapy in heart failure, some patients whose left ventricular ejection fraction (LVEF) initially increases on BB therapy experience a subsequent LVEF decline. This study aimed to evaluate the proportion of patients with non-ischemic cardiomyopathy (NICM) whose LVEF declines while on BB therapy and determine important predictors of LVEF decline.

Methods A retrospective analysis of 238 patients receiving a BB (carvedilol, metoprolol succinate, or tartrate), with an ejection fraction of $\leq 40\%$ and NICM, whose LVEF initially rose $\geq 5\%$ after 1 year of BB therapy, was conducted. Post-response LVEF decline $\geq 5\%$ to a final LVEF of $\leq 35\%$ was evaluated within 4 years of BB initiation.

Results In our study, we had 52 Caucasians (22%), 78 Hispanics (33%), and 108 African Americans (45%). Overall, 32 patients (13.44%) had post-response LVEF decline. The nadir LVEF of patients with post-response LVEF decline was 25% (interquartile range 20–27). Compared with others, Hispanics had lower nadir LVEF (22%, $p < 0.001$). Important predictors of LVEF decline were Hispanic race (odds ratio (OR) 6.094, $p < 0.001$), New York Heart Association (NYHA) class (OR 2.287,

$p < 0.05$), baseline LVEF (OR 1.075, $p < 0.05$), and age (OR 0.933, $p < 0.001$).

Conclusion A significant proportion (13.44%) of NICM patients with LVEF increase over 1 year of BB therapy experienced subsequent LVEF decline. Race, NYHA class, baseline LVEF, and age are important predictors of this decline.

1 Introduction

Heart failure (HF) is a major public health problem [1–3] with poor outcomes especially in African Americans (AA) and Hispanics [1, 4]. The higher mortality in these groups has been attributed to differences in the severity and causes of HF, the prevalence of coexisting conditions and risk factors [2], socioeconomic and cultural factors, and access to high-quality medical care [5].

Beta blockers (BBs) are beneficial in patients with symptomatic HF or left ventricular (LV) systolic dysfunction [6–8]. The increase in left ventricular ejection fraction (LVEF) is greater in patients with lower baseline LVEF after treatment with BB therapy [9, 10]. It has been suggested that after response to BB therapy, the BB should not be withdrawn, because of an increased risk of clinical deterioration or death from progressive congestive heart failure (CHF) [11].

However, response to BBs may vary among different ethnic groups [12–14]. There may be race-related genetic differences in the beta-adrenergic pathway explaining that difference. Differences such as the frequency of the G-protein-coupled receptor kinase (GRK)-Leu41 polymorphism, which desensitizes beta-adrenergic receptors, have been found between AA and Caucasian patients [15]. Overall, BBs have been shown to have similar benefits in both AA and Caucasians [16–20]. Previous HF studies

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have generally been limited to comparisons between AA and Caucasian populations [2, 12], but there are few comparative statistics concerning HF in Hispanics, one of the fastest-growing segments of the US population [21].

For patients who experience an improvement in ventricular performance on BB therapy, there is little data regarding whether this improved performance is maintained on continued BB therapy. Although several studies have shown improvements in mortality and hospitalizations for CHF over more than 2 years, there is little data following LVEF on BB therapy past 1 year [7, 8, 17, 19, 22, 23]. Of special interest is the effect of BBs on non-ischemic cardiomyopathy (NICM) since the effect of BBs on LVEF is often unpredictable in this group [7, 24]. Therefore, it is unknown with what frequency LVEF increase on BB therapy is maintained past 1 year in patients with HF. Moreover, while substantial information is available on racial differences in mortality and risk factors, much less is known about racial differences in LVEF response to BBs in patients with NICM.

This study aimed to examine the frequency of decline in LVEF after initial response to BB therapy in patients with NICM and to compare this frequency between AA, Hispanic, and Caucasian patients.

2 Methods

2.1 Study Population

A total of 238 patients with baseline a left ventricular ejection fraction (LVEF) of $\leq 40\%$ utilizing BBs (carvedilol, metoprolol succinate, or tartrate) with NICM who were followed at the HF clinic of Weiler Hospital of the Albert Einstein College of Medicine were analyzed retrospectively. Patients with ischemic and hypertrophic cardiomyopathy, hemodynamically significant valvular lesions, severe bronchospastic lung disease, baseline heart rate (HR) $< 60/\text{min}$ or systolic blood pressure (BP) $< 90\text{ mmHg}$ were excluded. Patients whose LVEF failed to rise by $\geq 5\%$ after 1 year of BB therapy were also excluded.

2.2 Study Design

The clinical design was a retrospective study aimed at analyzing the effects of BBs on LVEF response among a multi-ethnic population. Approval was granted from the Albert Einstein College of Medicine Institutional Review Board. BBs were titrated up to the maximum tolerable dose without a predefined time schedule. The maximum tolerable dose was the daily dose over which there was either (1) aggravation of dyspnea or edema, (2) systolic BP $< 90\text{ mmHg}$ or HR $< 60/\text{min}$ at rest, or (3) a need to increase the concomitant

medication for HF. The assignment of race was by self-report. LVEF was measured using 2-dimensional echocardiography and the modified Simpson's rule. The following measurements were taken: LVEF before BB therapy, LVEF after 1 year of BB therapy, and subsequent LVEF measurements while still on BB therapy after 1 year. As in previous studies [8, 25], LVEF responders to beta blockade were defined as patients with an absolute increase in LVEF $\geq 5\%$ after maximal doses of BB. The lowest LVEF at any time subsequent to the LVEF measurement at 1 year was noted. If the lowest subsequent LVEF was $\leq 35\%$ and was at least 5% lower than LVEF at the end of the first year of BB therapy, the term 'post-response LVEF decline' was assigned. A high dose of BB was defined similarly to prior studies [6–8]. For example, a high dose of metoprolol was defined as $\geq 150\text{ mg}$ oral (PO) daily, whereas a high dose of carvedilol was defined as $\geq 50\text{ mg}$ PO daily.

2.3 Statistical Analyses

Statistical analyses were performed using STATA version 12.0 statistical software. A p value of ≤ 0.05 was considered statistically significant. Continuous data are presented as median and interquartile range in variables that were not normally distributed, while categorical data are presented as number (percentage of patients). Comparisons between groups were made using two-sample t test, one-way ANOVA or the non-parametric equivalent for continuous variables and Chi-square test or Fisher's exact test for categorical data. Pearson and Spearman correlation coefficients (r) were used to quantify associations between variables. The effects of beta blockade on LVEF change after 1 year were compared using paired t test or the non-parametric equivalent. To determine important predictors of post-response LVEF decline, we also performed multi-variable logistic regression analysis.

3 Results

3.1 Clinical Characteristics

This study included 238 patients: 78 Hispanics, 108 AA, and 52 Caucasians. The clinical characteristics of the study cohort stratified by LVEF response are displayed in Table 1. Overall, the median age was 62 years. As shown, patients with post-response LVEF decline were predominantly Hispanics (44 vs. 29%, $p < 0.01$), and more often had intra-cardiac defibrillator (ICD) (56 vs. 27%, $p < 0.001$) compared with patients with sustained LVEF response.

Regarding medication use (Table 2), 142 patients (60%) received carvedilol, whereas 96 patients (40%) received metoprolol. The median dose of carvedilol was 25 mg daily,

Table 1 Clinical characteristics between patients with post-response LVEF decline and patients with sustained LVEF response

	All NICM responders (<i>N</i> = 238)	Post-response LVEF decline (<i>n</i> = 32)	Sustained LVEF response (<i>n</i> = 206)	<i>p</i> value
Males	126 (53 %)	14 (44 %)	112 (54 %)	0.263
Race				0.247
Caucasians	52 (22 %)	6 (19 %)	46 (22 %)	0.001
Hispanics	78 (33 %)	14 (44 %)	64 (31 %)	0.002
AA	108 (45 %)	12 (38 %)	96 (47 %)	0.842
Age (years)	62	55	62	0.014
Median,	(50.71)	(43.68)	(52.71)	
IQR				
Diabetes	106 (45 %)	12 (38 %)	94 (46 %)	0.389
HTN	166 (70 %)	24 (75 %)	142 (69 %)	0.487
NYHA class				0.14
I	32 (13 %)	2 (6 %)	30 (15 %)	
I–II	22 (9 %)	6 (19 %)	16 (8 %)	
II	90 (38 %)	10 (31 %)	80 (39 %)	
II–III	44 (18 %)	2 (6 %)	42 (20 %)	
>III	50 (21 %)	12 (38 %)	38 (18 %)	
ICD	74 (31 %)	18 (56 %)	56 (27 %)	0.001
Valvular disease	54 (23 %)	4 (13 %)	50 (24 %)	0.176
Dyslipidemia	156 (66 %)	20 (63 %)	136 (66 %)	0.697
CKD	48 (20 %)	4 (13 %)	44 (21 %)	0.245
Smoking	110 (46 %)	10 (31 %)	100 (49 %)	0.09
Alcohol	74 (31 %)	10 (31 %)	64 (31 %)	0.983

p value (Chi-square for categorical variables and Mann–Whitney test for continuous variables) for comparison between groups (post-response LVEF decline vs. sustained LVEF response)

AA African Americans, CKD chronic kidney disease, HTN hypertension, ICD intracardiac defibrillator, IQR interquartile range, LVEF left ventricular ejection fraction, NICM non-ischemic cardiomyopathy, NYHA New York Heart Association

whereas the median dose of metoprolol was 88 mg daily. As shown, compared with patients with sustained LVEF response, patients with post-response LVEF decline were on lower doses of carvedilol (25 vs. 37.5 %, $p < 0.01$) but not metoprolol. Regarding overall dose of BB (combined), there was no difference between the different LVEF response groups (higher vs. lower dose). Most of the patients (95 %) were on an angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB).

3.2 Left Ventricular Ejection Fraction (LVEF) Improvement After Beta Blockade

Among 238 patients with NICM, 32 (13 %) had post-response LVEF decline and 206 (87 %) had sustained LVEF response. Overall, there was a significant improvement of

LVEF from baseline after 1 year of BB (30–44 %, $p < 0.001$). Figure 1 shows change in LVEF after BB in patients with NICM within 4 years after the initial LVEF. There was no difference in the LVEF before initiation of BB in the two LVEF response groups (30 vs. 29 %, $p = 0.098$). Compared with patients with post-response LVEF decline, patients with sustained LVEF response had a higher LVEF at 1 year (47 vs. 41 %, $p < 0.01$) and a higher nadir of LVEF (40 vs. 25 %, $p < 0.001$).

Table 3 shows differences in change in LVEF between different races. Compared with other races, Hispanics had lower LVEF increase after 1 year of BB (40 %, $p < 0.01$) and lower nadir LVEF in both the post-response LVEF decline group (22 %, $p < 0.001$) and sustained LVEF response group (32 %, $p < 0.01$) (Fig. 2). There was no difference in the percentage of sustained and post-response LVEF decline between races.

3.3 Predictors of Post-Response LVEF Decline

Table 4 shows results of the multivariable logistic analysis using post-response LVEF decline as the outcome of interest. Hispanic race was a significant predictor of LVEF decline in both unadjusted (odds ratio (OR) = 3.128, $p < 0.01$) and adjusted analyses (OR 6.094, $p < 0.001$). Age (OR 0.933, $p < 0.001$) and baseline LVEF (OR 1.075, $p < 0.05$) also remained significant predictors of post-response LVEF decline. Gender, New York Heart Association (NYHA) class, use of an ACEI/ARB, and dose of BB were not significant predictors of LVEF decline. Similar results were noted when we examined the post-response LVEF decline at 1 year (data not shown).

4 Discussion

This study aimed to examine the frequency of decline in LVEF after initial response to BB therapy and to compare this frequency between AA, Hispanic, and Caucasian patients. The primary finding of this study was that there might be a significant proportion of HF patients whose LVEF declines after initially responding to BB therapy. This conclusion is drawn from the observed occurrence of LVEF decline after initial response to BB therapy at a rate of 13.44 % over 4 years after the initiation of therapy. Compared with other races, Hispanics had lower nadir LVEF (22 %, $p < 0.001$). Important predictors of LVEF decline were Hispanic race, NYHA class, baseline LVEF, and age, but not gender.

In our study, we found that there seems to exist an occurrence of LVEF decline after initial response to BB therapy at a rate of 13.44 % over 4 years after the initiation of therapy in patients with NICM. Prior studies have shown

Table 2 Differences in medications between patients with post-response LVEF decline and patients with sustained LVEF response

Medications	All NICM responders after 1 year of BB (<i>N</i> = 238)	Post-response LVEF decline (<i>n</i> = 32)	Sustained LVEF response (<i>n</i> = 206)	<i>p</i> value
Carvedilol	142 (60 %)	24 (75 %)	118 (57 %)	0.06
Median-dose carvedilol (mg) (range of dose)	25 (18.75–50)	25 (12.5–25)	37.5 (25–50)	0.020
Low-dose carvedilol (6.25 mg PO bid) (<i>n</i> , %)	35 (15 %)	9 (28 %)	26 (13 %)	0.021
Medium-dose carvedilol (12.5 mg PO bid)	49 (21 %)	11 (34 %)	38 (18 %)	0.038
High-dose carvedilol (25 mg PO bid)	58 (24 %)	4 (13 %)	54 (26 %)	0.093
Metoprolol	96 (40 %)	8 (25 %)	88 (43 %)	0.06
Median-dose metoprolol (mg)	87.5 (50–100)	75 (37.5–150)	87.5 (50–100)	0.811
Low-dose metoprolol (25 mg PO bid)	48 (20 %)	4 (13 %)	44 (21 %)	0.245
Medium-dose metoprolol (50 mg PO bid)	27 (11 %)	2 (6 %)	25 (12 %)	0.329
High-dose metoprolol (>75 mg PO bid)	21 (9 %)	2 (6 %)	19 (9 %)	0.581
Overall dose of BB (combined)				
Low	83 (35 %)	13 (41 %)	70 (34 %)	0.463
Medium	76 (32 %)	13 (41 %)	63 (31 %)	0.257
High	79 (33 %)	6 (19 %)	73 (35 %)	0.062
ACEI or ARB	226 (95 %)	30 (94 %)	196 (95 %)	0.737
Hydralazine	40 (17 %)	2 (6 %)	38 (18 %)	0.086
Nitrates	32 (13 %)	0 (0 %)	32 (16 %)	0.017
Spirolactone	134 (56 %)	22 (69 %)	112 (54 %)	0.127
Digoxin	120 (50 %)	14 (44 %)	106 (51 %)	0.417
Calcium channel blocker	42 (18 %)	4 (13 %)	38 (18 %)	0.412

p value (Chi-square for categorical variables and Mann–Whitney test for continuous variables) for comparison between groups (post-response LVEF decline vs. sustained LVEF response)

ACEI Angiotensin-converting enzyme inhibitors, ARB angiotensin II receptor blockers, BB beta blocker, *bid* twice daily, LVEF left ventricular ejection fraction, NICM non-ischemic cardiomyopathy, PO oral

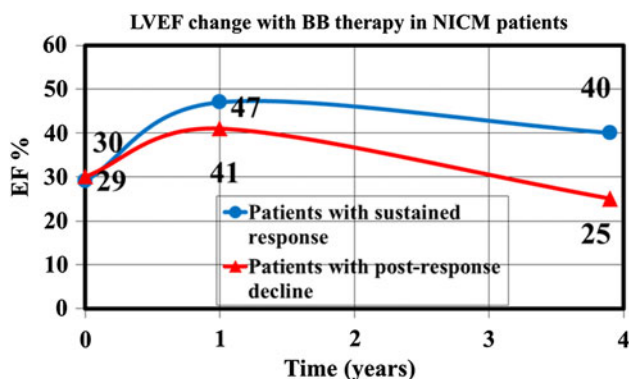


Fig. 1 Change in LVEF after BB in patients with NICM. Compared with patients with post-response LVEF decline, patients with sustained LVEF response had higher LVEF at 1 year (47 vs. 41 %, $p < 0.01$) and higher nadir of LVEF (40 vs. 25 %, $p < 0.001$). BB beta blocker, LVEF left ventricular ejection fraction, NICM non-ischemic cardiomyopathy

that patients with NICM may respond better to BBs than patients with ischemic cardiomyopathy [26–28]. Patients with NICM have initially increased wall tension due to dilated LV that causes increased myocardial oxygen demands. The global subendocardial ischemia might form

a homogeneous substrate for BB action. Therefore BBs may find a more homogeneous substrate in the first months after initiation of therapy. During therapy and maybe over time because of changes in wall stress, this substrate may change and the effect of BBs in LVEF declines. Another factor that may explain the percentage of post-response LVEF decline in patients with NICM may be genetic variability. Prior studies have shown that patients with certain beta receptor genotypes were associated with better clinical response to BBs compared with others [15, 29–32]. Perhaps the patients with post-response LVEF decline have different polymorphisms than the patients with sustained LVEF response. Future research aimed at analyzing polymorphisms among patients with NICM who do not seem to have a sustained response to BBs may yield interesting results.

Interestingly, we found that Hispanics with chronic HF had worse LVEF response and post-response LVEF decline after use of a BB compared with other races. To our knowledge this is one of the first studies to examine differences in LVEF response between AA and Hispanics with NICM. Although the Hispanic population has been shown to comprise a high-risk cardiovascular group [33–

Table 3 Differences in change in LVEF between different races (patients with post-response LVEF decline and patients with sustained LVEF response)

	All NICM (<i>N</i> = 238)	Caucasians (<i>n</i> = 52)	Hispanics (<i>n</i> = 78)	AA (<i>n</i> = 108)	<i>p</i> Value
Post-response LVEF decline [<i>n</i> (%)]	32	6 (19)	14 (44)	12 (38)	0.288
Baseline LVEF before BB [median (IQR)]	30 (24–35)	34 (24–42)	32 (22–36)	27 (19–31)	0.024
LVEF after 1 year of BB [median (IQR)]	41 (29–52)	47 (35–50)	40 (30–48)	45 (36–52)	<0.01
Post-response nadir LVEF [median (IQR)]	25 (20–29)	27 (20–31)	22 (20–25)	26 (24–32)	<0.01
Sustained LVEF response [<i>n</i> (%)]	206	47 (23)	60 (29)	99 (48)	0.147
Baseline LVEF before BB [median (IQR)]	29 (23–36)	27 (22–30)	30 (20–38)	30 (25–35)	0.036
LVEF after 1 year of BB [median (IQR)]	47 (35–54)	49 (38–55)	38 (22–41)	44 (34–48)	<0.01
Post-response nadir LVEF [median (IQR)]	40 (25–44)	42 (31–46)	32 (25–37)	36 (28–40)	0.005

p value for comparison of different races

AA African Americans, BB beta blocker, IQR interquartile range, LVEF left ventricular ejection fraction, NICM non-ischemic cardiomyopathy

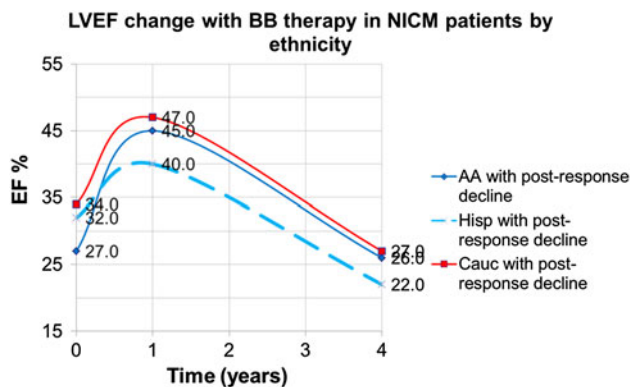


Fig. 2 Change in LVEF after BB in patients with NICM. Compared with other races, Hisp had a lower LVEF increase after 1 year of BB ($p < 0.01$) and lower nadir LVEF in both the post-response LVEF decline group (22 %, $p < 0.01$) and sustained LVEF response group (32 %, $p < 0.01$). AA African Americans, BB beta blocker, Cauc Caucasians, Hisp Hispanics, LVEF left ventricular ejection fraction, NICM non-ischemic cardiomyopathy

35], there are very limited data on Hispanic patients with chronic systolic HF. AA have been underrepresented in major HF trials, whereas Hispanic patients have been nearly absent in most clinical trials, and thus there are very limited data regarding the effect of medications such as BBs in this ethnic group. Although LVEF patterns in Hispanic subgroups compared with non-Hispanic whites have been examined in the MESA (Multi-Ethnic Study of Atherosclerosis) [34, 35], these patterns have not been associated with use of BBs. In our study, we confirm prior findings that Hispanics have differences in clinical response of HF parameters compared with other races [36]. Finally, we extended this finding by showing that Hispanics have worse LVEF response and post-response LVEF decline compared with other races after use of BBs.

The different LVEF response to BBs among races can be explained by a few factors [12–14]. A difference in LVEF response and LVEF decline can be explained by differences

Table 4 Important predictors of post-response LVEF decline (multivariable logistic regression). Final models adjusted for important clinical characteristics such as age, gender, NYHA class

Predictors	Post-response LVEF decline (<i>n</i> = 32)			
	Unadjusted		Adjusted	
	OR	<i>p</i> value	OR	<i>p</i> value
Baseline LVEF (overall)	1.047	0.038	1.075	0.029
Race (white is reference)				
Hispanic race	3.128	0.003	6.094	<0.001
AA	0.926	0.842	0.595	0.224
NYHA class	1.431	0.240	2.287	0.035
BB dose (low dose of BB is reference)				
Medium-dose BB	1.553	0.259	1.220	0.687
High-dose BB	0.420	0.069	0.312	0.063
ACEI/ARB	0.765	0.738	0.532	0.472
Gender	0.652	0.265	0.951	0.910
Age	0.960	0.005	0.933	<0.001

AA African Americans, ACEI angiotensin-converting enzyme inhibitors, ARB Angiotensin II receptor blockers, BB beta blocker, LVEF left ventricular ejection fraction, NYHA New York Heart Association, OR odds ratio

among ethnic groups with respect to ancestry/race [37], socioeconomic factors [5], and dietary and lifestyle risk factors for cardiovascular disease [38]. However, our study was not designed to explain why LVEF response and LVEF decline seems to differ in different ethnic subgroups and socioeconomic status was not one of the predictors of LVEF decline. Similar to other studies [17–20], we found that AA and Caucasians had similar response to BBs after 1 year and similar post-response LVEF decline. However, other studies such as the beta-blocker evaluation of survival trial (BEST) showed that AA patients had a worse HF prognosis than Caucasians because of genetic differences [20]. A genetic substudy of the BEST data, which evaluated the effects of BBs among differing B-gene polymorphisms

showed that patients with certain beta receptor genotypes were associated with the better clinical response to BBs compared with others [15, 29–32]. Another study showed that carvedilol significantly increased LVEF in CHF patients with the Glu(27)beta(2)-adrenergic receptor allele [39]. Therefore differences in LVEF response to BBs [40, 41] could be attributed to genetic differences. Hispanic patients with NICM may have genetic polymorphisms that could explain why this racial group may be more susceptible to post-response LVEF decline compared with other races. In this regard, the interactions between Hispanic race, care-seeking behavior, and access to high-quality HF care remain important areas for future investigation, and future research aimed at analyzing polymorphisms among Hispanics and AA may yield interesting results.

Whether there is any variable that can predict maintenance of LVEF after initial response to BB therapy in patients with HF remains to be discovered. Our study showed that age and NYHA class were important predictors of LVEF response compared with other predictors such as BB dose. These results are consistent with prior studies that have shown that age and NYHA class have a strong association with LVEF response to BBs [14, 22]. Regarding dosing of BBs, in the multicenter oral carvedilol heart failure assessment (MOCHA) trial, carvedilol (12.5–50 mg/day) generated dose-related LVEF improvement (5–8 %) in HF patients, of whom 77 % were Caucasians [7]. The carvedilol dose in our patients was about the same dose as that used in the MOCHA trial, but the magnitude of the LVEF improvement for Caucasians in our study was higher. Although this finding is consistent with other studies [10, 42, 43], to the best of our knowledge there are no prior studies regarding BB dosing and LVEF response in Hispanics. In our study, we also confirmed the finding that the effect of BBs on LVEF response was similar irrespective of type of BB used (metoprolol or carvedilol) [10, 42, 43]. Therefore, Hispanics with NICM may have worse post-response LVEF decline irrespective of BB dose and type of BB used compared with other races. Given that prior data have shown differences in LVEF response to BBs [15, 29–32, 40, 41] due to genetic differences (B-gene polymorphisms), genetic background might explain variation in post-response LVEF decline [15].

Finally, baseline LVEF was an important predictor of post-response LVEF decline. Our data is consistent with prior studies that have shown that baseline LVEF has a significant association with response to BB therapy [9, 10]. The increase in LVEF is greater in patients with lower baseline LVEF after treatment with BB therapy [9]. The down-regulation of beta-1-receptor density may be greater with higher chronic catecholamine exposure, which may be

the case with more severe cardiomyopathy [10]. BB therapy may then up-regulate beta-1-receptor density to a greater extent in these more severe disease states.

Due to the retrospective nature of the study, expected limitations were encountered. The number of patients enrolled in this study precluded restriction of analyses to only those with low ejection fraction or only those with symptoms of HF. Those variables that were determined by self-report or review of the medical records are beyond the control of the investigators and, thus, subject to error. There was also a lack of availability of data on medical therapy and a lack of information regarding socioeconomic status, including education and income, that may have had an effect on HF outcomes. In addition, this is a single-center study and the findings may not confer external validity. In our Hispanic population, we did not identify special subgroups such as Mexican-origin Hispanics versus those of Caribbean-origin, subgroups which have been shown to have differences in LV remodeling parameters [34, 35]. Finally, the methods used in this study serve only to describe statistical associations between variables, which are not necessarily proof of causation.

5 Conclusion

A significant proportion (13.44 %) of NICM patients who experienced an improvement in LVEF with BB therapy in the first year had a subsequent decline. Race, NYHA class, baseline LVEF, and age are important predictors of post-response LVEF decline. An underlying genetic difference may explain differences in LVEF response to BB therapy observed in this study. Future studies should evaluate genetic polymorphisms affecting beta-adrenoceptor function in patients with NICM.

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