MANUSCRIPT RESPONSES AND REVISIONS
Response to Reviewer # 1. The authors appreciate the carefully considered comments provided by the reviewer. We have addressed these comments as follows:

The reviewer expressed concern regarding the use of the ROC curve. As the reviewer notes, there are different applications of the curve. We have used the curve as a means to assess the discriminatory capacity of the resultant model based on the data analyzed. This is a valid and commonly used application of this technique in the process of model development, as stated in reference 12 of the manuscript. In this sense, it is the area under the curve that is informative regarding the model performance. The area under the curve reflects the capacity of a model to assign a higher probability of the outcome of interest to covariate sets corresponding to subjects who in fact have the outcome. The curve is not taken as a representation of model sensitivity and specificity based on specific points on the curve. As the reviewer notes, this would have no real meaning given the fact that subjects were specifically selected based on presence or absence of the end-point of interest. To avoid possible confusion regarding this point, we have removed the illustration of the ROC curve, and simply state the area under the curve in the results section of the manuscript.
The model’s capacity to discriminate subjects with recovery of ventricular function from those without recovery was tested by the area under the receiver operating characteristic curve. This area was found to be 0.88 indicating excellent discriminatory capacity of the model. The mean variance inflation factor for variables included in the final model was 1.3 consistent with negligible collinearity among the final model variables.
The reviewer questions the relevance of the reported findings to the application of biventricular pacing. The authors agree that this is a speculative aspect of the discussion and extends beyond the primary focus of the investigation. Accordingly, we have deleted comments related to this speculation on pages 10 and 12 of the revised manuscript (indicated by strike-through text). We have retained the comment that the mean QRS duration in the non-recovered group was 120 msec simply noting this as an interesting observation.
Of importance, there is little overlap between the range of QRS durations for the patients who recovered and those who did not. The mean and standard deviation of the QRS interval for those who recovered ventricular function was 98 ± 4 msec indicating that two standard deviations above the mean for this group is 106 msec. For the non-recovered patients, the standard deviation was 4 msec indicating that two standard deviations below the mean is 112 msec. This implies that there may be a significant proportion of patients with QRS durations in the range of 106 to 120 msec who could benefit from cardiac resynchronization. This observation further supports ongoing clinical trials investigating initiation of biventricular pacing at shorter QRS durations than currently accepted.
Interestingly, the mean QRS duration in the subjects who did recover ventricular function was 120 msec which is precisely the value currently accepted as discriminating between patients who should and should not undergo biventricular pacing. Similar to the case for systolic blood pressure, the odds ratio of 0.95 in the final model indicates that there is a reduced odds of recovery for any given QRS interval compared to an interval 1 msec shorter. Again, the difference in odds is amplified over larger differences such that an increase in QRS duration from 90 msec to 120 msec is associated with a reduced odds ratio of 0.22 for recovery ($\exp(0.05(90-120))$).
1. The reviewer appropriately notes that this is a case control study. Such study designs can identify both cases and controls in a prospective as well as retrospective fashion. This is of course different from a prospective cohort trial in which the end-point of interest has not yet occurred in the study sample. To avoid confusion, we have deleted the term prospective in the first paragraph of the Methods section. We have instead stated that patients were “observed during the course of clinic follow up” to have an increase in ejection fraction to 40% or greater. Similar wording has been used in the revised abstract. We have eliminated the term “prospective” in the first line of the Experimental Limitations section of the Discussion and have deleted the sentence in that same section discussing prospective identification of subjects.
Fifty-three patients with symptomatic AHA/ACC stage C congestive heart failure having ejection fractions less than 35% who were followed in the Ohio State University Heart Failure Clinic and who were observed during the course of clinic follow up to have an increase in ejection fraction as measured by echocardiographic studies to 40% or greater constituted the study population.
Experimental Limitations. As noted, this investigation employed a prospective case control design and is subject to the limitations inherent in such studies. However, measures were taken to minimize such limitations. Although a case control design was used, it was a prospective investigation in that patients who recovered normal ventricular function were identified in the course of clinic follow-up, not through a retrospective examination of clinic case records. Control subjects were selected using the technique of frequency
As the reviewer notes, we have discussed that QRS duration may in some ways serve as a surrogate for ventricular volumes. Based on the reviewer’s suggestions, we tested echocardiographically derived dimensions and volumes in the logistic regression model. The dimensions and volumes were not significant in the context of the model and did not add to the overall significance of the model. This is consistent with our discussion in the Experimental Limitations section of the original manuscript regarding the probable redundancy of information contained in both the QRS width and ventricular volumes. Owing to the fact that this did not contribute significantly to the model and considering word limitations of the manuscript, we have not included this observation in the revised manuscript.
The reviewer is correct that many of the variables retained in the final model have clinical associations. In particular, female gender may tend to be more highly associated with non-ischemic etiology, diabetes may be associated with ischemic disease, and those with hypertension may have hypertensive rather than ischemic cardiomyopathy. We have addressed this important issue in the revised Discussion section on page 11 of the manuscript. The forward selection algorithm prevents inclusion of variables that are collinear or effectively represent the same information contributing to the association with recovery of ventricular function. If such collinearity exists between two variables, their coefficients would not both be significant when included in the model. Similarly, the absence of significant interaction and confounding reflects the independent contribution of the variables to recovery of ventricular function despite their possible clinical interrelation.
Some variables retained in the final model have an expected clinical interrelation. Women have a later onset of coronary artery disease and therefore may tend to have cardiomyopathy on a non-ischemic basis especially when considering younger populations. Similarly, patients with diabetes may be more likely to have associated ischemic cardiomyopathy owing to their propensity to atherosclerosis. Conversely, patients with a higher blood pressure may have reduced ventricular function on the basis of hypertensive cardiomyopathy rather than due to ischemia. However, the forward selection modeling process identified the final variables as being independently associated with recovery of ventricular function even in the context of other variables. The fact that many variables with individual significant associations with recovery of ventricular function (Table 1) were not retained in the final model demonstrates the capacity of the modeling process to identify variables that independently contribute to the odds of ventricular recovery. The absence of confounding and interaction among the final model variables further indicates that, despite clinical associations, these variables retain their own unique contribution to the probability of restoration of normal ventricular function.
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OTHER RESPONSES

• Addressed Issue of How Ejection Fraction Measured
• Addressed occurrence of MI and other clinical variables in a new table of clinical characteristics
To the Editor:
Thank you for your interest in our manuscript “Recovery of Normal Ventricular Function in Patients with Dilated Cardiomyopathy: Predictors of an Increasingly Prevalent Clinical Event” (manuscript number AHJ740497). In response to the reviewers’ thoughtful comments, we have extensively revised the manuscript. As requested, we have indicated revisions in the text of the revised manuscript by strike through font for deletions and italic text for additions. The specific revisions are discussed in the response to the reviewers which are keyed to the numbered items in their comments. The following is a summary of the revisions which are discussed in more detail in the response to the reviewers: 1. The discussion of implications of the findings regarding patients responding to biventricular pacing has been deleted; 2. We have removed the ROC curve illustration and address in the response to the reviewer the use of this curve in the context of the modeling process; 3. We have added a new table summarizing the clinical characteristics of the two patient groups; 4. We have removed reference to the study design as being prospective and deleted this discussion from the Experimental Limitations section; 5. We have clarified the history of myocardial infarction in the patient cohort; 6. We have addressed the issue of possible clinical interrelationship of the final model variables;
7. We have statistically analyzed the impact of measures of ventricular dimensions and volumes and discussed in the response to the reviewer the findings of this analysis; 8. We have clarified the exclusive use of echocardiographic measures for the determination of ejection fraction and emphasized the consistency of the techniques of measurement; 9. We have addressed in the response to the reviewer the issue of the mean time to recovery of ventricular function and its relation to the process of ventricular remodeling; 10. We have addressed the issue of consistent drug administration in accordance with expert recommendations existing at the time of the patient enrollment and the consistency of drug administration throughout the study period.
Table 1. Characteristics of the Study Sample

<table>
<thead>
<tr>
<th></th>
<th>Not Recovered</th>
<th>Recovered</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline EF</td>
<td>18 ± 6%</td>
<td>18 ± 6%</td>
<td>18 ± 6%</td>
</tr>
<tr>
<td>Final EF</td>
<td>22 ± 8% **</td>
<td>55 ± 7% *++</td>
<td>40 ± 18%</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>51.3 ± 10.2</td>
<td>43.0 ± 13.0 *</td>
<td>47.1 ± 12.3</td>
</tr>
<tr>
<td>QRS (msec)</td>
<td>120 ± 27</td>
<td>98 ± 25 *</td>
<td>109 ± 28</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.38 ± 0.70</td>
<td>1.06 ± 0.47 *</td>
<td>1.23 ± 0.62</td>
</tr>
<tr>
<td>Sys BP (mmHg)</td>
<td>115 ± 21</td>
<td>124 ± 22 *</td>
<td>119 ± 22</td>
</tr>
<tr>
<td>Dias BP (mmHg)</td>
<td>70 ± 13</td>
<td>73 ± 15 *</td>
<td>72 ± 14</td>
</tr>
<tr>
<td>Ischemic CM (%)</td>
<td>53</td>
<td>17 *</td>
<td>35</td>
</tr>
<tr>
<td>Female (%)</td>
<td>19</td>
<td>56 *</td>
<td>38</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>40</td>
<td>21 *</td>
<td>31</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>19</td>
<td>44 *</td>
<td>32</td>
</tr>
</tbody>
</table>

* = p < 0.05 comparing recovered and not recovered groups; ++ = p < 0.05 compared to baseline; EF = ejection fraction; QRS = Electrocardiographic QRS interval; Sys BP = Systolic Blood Pressure; Dias BP = diastolic blood pressure; Ischemic CM = Ischemic Cardiomyopathy; Diabetes = history of diabetes; HTN = history of hypertension
DECISION?

• Accept with Current Revisions?
• Request Further Changes?
• Reject?
Dear Dr. Binkley:

We have completed our review of your manuscript, AHJ70497R1, "Recovery of Normal Ventricular Function in Patients with Dilated Cardiomyopathy: Predictors of an Increasingly Prevalant Clinical Event" and we are pleased to accept it.

Thank you for submitting your manuscript to the American Heart Journal.

Sincerely,

Daniel B. Mark, M.D., M.P.H., Editor