Author’s response to reviews

Title: Prediction of Left Ventricular Reverse Remodeling after Therapy with Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers and beta Blockers in Patients with Idiopathic Dilated Cardiomyopathy

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Version: 3
Date: 3 March 2015

Author’s response to reviews: see over
Response to referee' comments

Referee 1: The authors assessed the left ventricular reverse remodeling after therapy with angiotensin converting enzyme inhibitors or angiotensin-receptor blockers and # blockers in patients with idiopathic dilated cardiomyopathy. Study population included 44 patients with idiopathic dilated cardiomyopathy. The authors concluded that combined information on LV end-diastolic dimension and heart rhythm at diagnosis is useful in predicting future left ventricular reverse remodeling in patients with idiopathic dilated cardiomyopathy. The paper is interesting. However, some points should be clarified.

1. The study population is too small (only 44 patients)
2. The authors should report in the table type and dose of angiotensin converting enzyme inhibitors or angiotensin-receptor blockers and beta blockers
3. All patients were in therapy with beta blockers and angiotensin converting enzyme inhibitors or angiotensin-receptor blockers: the authors should analyzed the role of the specific therapy on LVRR
4. The authors should add a table included the variables used in the univariate and multivariate regression analysis
5. Atrial fibrillation was present in only 10 patients, without difference between the 2 groups (LVRR+ and-), and the authors reported in the discussion: “...First, the presence of atrial fibrillation tended to be associated with LVRR”... and they concluded: “...The presence of atrial fibrillation tended to be associated with future LVRR....”. The authors should focus the discussion and conclusions only on the variables significantly different between the 2 studied groups.

1. The study population is too small (only 44 patients)
I agree with the referee’s comment. I have corrected the identical sentences in the last section of Discussion, as follows: Further studies with a large number of patients are required to confirm the results of the present study (revised manuscript, page 13, line 2-3).

2. The authors should report in the table type and dose of angiotensin converting enzyme inhibitors or angiotensin-receptor blockers and beta blockers
According to the referee’s suggestion, I have corrected the identical sentences in the Results, as follows: There were no significant differences in the frequency of use of ACE inhibitors or ARBs. We most frequently used enalapril (83%) (30/36) as an ACE inhibitor and losartan (63%) (5/8) as an ARBs. There were no significant differences in these maintenance doses
between the 2 groups. Carvedilol was administered in 37 patients and metoprolol in 7 patients. There were no significant differences in the frequency of use of these drugs. There were no significant differences in these maintenance doses between the 2 groups (Table 1) (revised manuscript, page 8, line 7-12). I have also corrected Table 1. Furthermore, I have added the identical sentences in the last section of Discussion, as follows: The targeting doses of ACE inhibitors, ARBs, and β blockers were lower in the present study than those in the United States’ guidelines [26]. A low dose of carvedilol of 5 mg/day was beneficial in Japanese patients with heart failure in the Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial [27]. We have previously reported that low doses of ACE inhibitors, ARBs, and β blockers had favorable effects on the prognosis of Japanese patients with IDC [28,29]. The Japanese Guidelines (available at the Japanese Circulation Society Web site (http://www.j-circ.or.jp/) have recommended a targeting dose of enalapril of 5 to 10 mg/day and of carvedilol of 5 to 20 mg/day (revised manuscript, page 12, line 5-12). I have added new references (#26-#29).

3. All patients were in therapy with beta blockers and angiotensin converting enzyme inhibitors or angiotensin-receptor blockers: the authors should analyzed the role of the specific therapy on LVRR

In general, therapy with beta blockers and angiotensin converting enzyme inhibitors or angiotensin-receptor blockers block the neurohormonal activation and can cause left ventricular reverse remodeling. In the present study, we most frequently used enalapril (83%) as an ACE inhibitor and losartan (63%) as an ARB. There were no significant differences in these maintenance doses between the 2 groups. Carvedilol was administered in 37 patients and metoprolol in 7 patients. There were no significant differences in the frequency of use of these drugs. There were no significant differences in these maintenance doses between the 2 groups. Therefore, it is not possible to analyze the role of the specific therapy on LVRR. I have just corrected the identical sentences in the Discussion, as follows: Although the ACE inhibitors or ARBs and β blockers that block the neurohormonal activation play an important role in inducing LVRR (revised manuscript, page 10, line 5-6).

4. The authors should add a table included the variables used in the univariate and multivariate regression analysis

Univariate logistic regression analysis was used to determine a significant predictor of LVRR. Initial LVDd ≤ 63 mm with atrial fibrillation was a significant predictor of LVRR by univariate logistic regression analysis (odds ratio, 5.78; 95% confidence interval, 1.19 – 28.0, p = 0.030) (sensitivity: 33%, specificity: 97%, p = 0.013). I have corrected the identical
sentences in the Methods, as follows: **Univariate** logistic regression analysis was used to determine a significant predictor of LVRR (revised manuscript, page 7, line 12-13).

5. Atrial fibrillation was present in only 10 patients, without difference between the 2 groups (LVRR+ and-), and the authors reported in the discussion: “...First, the presence of atrial fibrillation tended to be associated with LVRR”... and they concluded: “...The presence of atrial fibrillation tended to be associated with future LVRR....”. The authors should focus the discussion and conclusions only on the variables significantly different between the 2 studied groups.

According to the referee’s suggestion, I have deleted “The prevalence of atrial fibrillation tended to be higher (40% vs. 14%, p = 0.067)” and “The presence of atrial fibrillation tended to be associated with LVRR (sensitivity: 40%, specificity: 86%, p = 0.067).” in the all sections of my manuscript and focus the discussion and conclusions only on the variables significantly different between the 2 studied group. I have corrected the identical sentences in Abstract, as follows: The presence of atrial fibrillation was 40% in patients with LVRR and 14% in those without (p = 0.067) (revised manuscript, page 2, line 10-11).
Referee 2: Matsumura et al sought to identify predictors of LV reverse remodeling (LVRR) after therapy with ACE-I/ARBs and beta blockers in a group of 44 patients with idiopathic dilated cardiomyopathy. I have several comments related to this article. The idea is not new, the authors themselves have published before on this topic and the number of patients is relatively limited.

Major Compulsory Revisions

1. It is not clear why the LVRR in this setting was defined as normalization of left ventricular size and contractility (LV end-diastolic dimension # 55 mm and fractional shortening # 25% at the last echocardiogram) since the same group reported in 2013 that LVRR, even if it is not marked, is associated with a favorable prognosis in this setting. (Matsumura et al. Am J Cardiol 2013;111:106-10).

The same conclusion was also reported before by Merlo et al. in 244 patients (Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. J Am Coll Cardiol 2011;57:1468-76.) The main result of their study was the observation that about one-third of patients with IDCM surviving 2 years showed LVRR at mid-term follow-up on tailored medical therapy and there was not only a clear prognostic value of the complete left ventricular contractility and dimension restoration, but also a role for progressive improvement of left ventricular dysfunction and dilation during the mid-term follow-up for all the major cardiovascular events related to IDCM.

2. Moreover, since the timing of the follow-up visits in the current study was quite variable (mean follow-up period of 4.7 ± 3.3 years, range 5 months to 12 years) it would have been more suitable to define LVRR as a percentage decrease in LV size and increase in LV function.

3. It is also not clear why the authors decided to use LV diameters in absolute values and LV FS as echocardiographic criteria for the diagnosis of IDCM and LVRR instead of using indexed LV diameters/volumes and LVEF? This should be explained and the analysis repeated.

4. The statement that „this is the first article that presents a predictor of LVRR in patients with IDC after therapy with ACE inhibitors or ARBs and # blockers” does not hold true. Kubanek et al. published in 2013 a study on predictors of LVRR in 44 pts with IDC and more than 90% of these pts were receiving ACE and beta blockers. (Kubanek M, et al. Novel predictors of left ventricular reverse remodeling in individuals with recent-onset dilated cardiomyopathy. J Am Coll Cardiol 2013;61:54-63.)

5. The correlation between atrial fibrillation and LVRR was not statistically significant in the present study („The prevalence of atrial fibrillation tended to be higher in patients with LVRR than in those without, 40% vs. 14%, p = 0.067”) and the pathophysiological
scenario proposed by the authors as an explanation for their finding is not very convincing. A higher sample size would be needed to clarify this issue.

1. It is not clear why the LVRR in this setting was defined as normalization of left ventricular size and contractility (LV end-diastolic dimension ≤ 55 mm and fractional shortening ≥ 25% at the last echocardiogram) since the same group reported in 2013 that LVRR, even if it is not marked, is associated with a favorable prognosis in this setting. (Matsumura et al. Am J Cardiol 2013;111:106-10).

The same conclusion was also reported before by Merlo et al. in 244 patients (Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. J Am Coll Cardiol 2011;57:1468-76.) The main result of their study was the observation that about one-third of patients with IDCM surviving 2 years showed LVRR at mid-term follow-up on tailored medical therapy and there was not only a clear prognostic value of the complete left ventricular contractility and dimension restoration, but also a role for progressive improvement of left ventricular dysfunction and dilation during the mid-term follow-up for all the major cardiovascular events related to IDCM.

We defined LVRR, which is normalization of LV systolic function, as LVDd ≤ 55 mm and LVFS ≥ 25% at the last echocardiographic assessment in our previous 2 papers (Am J Cardiol. 2011;107:1065-70) (Am J Cardiol 2013;111:106-10). As the referee has pointed out, our recent study suggested that LVRR, even if it is not marked, is associated with a favorable prognosis. Indeed, the prognosis of patients with not-marked LVRR could be better than that of patients with no LVRR. However, further follow-up of our patients and subgroup analysis might suggest that prognosis of patients with not-marked LVRR would be probably worse than that of patients with marked LVRR defined as LVDd ≤ 55 mm and LVFS ≥ 25%. On the other hand, there is a significant difference in beta blocker use between our study and study by Merlo et al. (J Am Coll Cardiol 2011;57:1468-76). Beta blocker use was 35% (85/242) in the study by Merlo et al.. I think that one of the goals of treatment is normalization of LV systolic function in patients with dilated cardiomyopathy. Therefore, we use the same LVRR definition as before. I have added the identical sentences in Methods, as follows: LV reverse remodeling (LVRR) was defined as described previously (LV end-diastolic dimension (Dd) ≤ 55 mm and fractional shortening (FS) ≥ 25% at the last echocardiogram) [5,10] (revised manuscript, page 7, line 1-3).

2. Moreover, since the timing of the follow-up visits in the current study was quite variable (mean follow-up period of 4.7 ± 3.3 years, range 5 months to 12 years) it would
have been more suitable to define LVRR as a percentage decrease in LV size and increase in LV function.

As the referee suggested, it would be suitable to define LVRR as a percentage decrease in LV size and increase in LV function. Percentage decrease or change in LV size would be suitable to predict future LVRR as we previously reported (Am J Cardiol. 2011;107:1065-70). I think that one of the goals of treatment is normalization of LV systolic function in patients with dilated cardiomyopathy. Therefore, we use the same LVRR definition as before.

3. It is also not clear why the authors decided to use LV diameters in absolute values and LV FS as echocardiographic criteria for the diagnosis of IDCM and LVRR instead of using indexed LV diameters/volumes and LVEF? This should be explained and the analysis repeated.

As the referee suggested, indexed LV diameters/volumes and LVEF would be theoretically suitable. However, the present study was retrospective and echocardiography was performed in routine clinical practice. Thus, indexed LV diameters/volumes and LVEF were not available. I have stated in Discussion, as follows: although all patients showed basically diffuse LV wall motion abnormalities, calculated LVFS would not be a representative estimate of systolic function, particularly when regional abnormalities were present (revised manuscript, page 12, line 14-16).

4. The statement that „this is the first article that presents a predictor of LVRR in patients with IDC after therapy with ACE inhibitors or ARBs and # blockers” does not hold true. Kubanek et al. published in 2013 a study on predictors of LVRR in 44 pts with IDCM and more than 90 % of these pts were receiving ACE and beta blockers. (Kubanek M, et al. Novel predictors of left ventricular reverse remodeling in individuals with recent-onset dilated cardiomyopathy. J Am Coll Cardiol 2013;61:54-63.)

As the referee pointed out, the statement that this is the first article that presents a predictor of LVRR in patients with IDC after therapy with ACE inhibitors or ARBs and beta blockers does not hold true. I have deleted the sentences and revised in Discussion, as follows: The present study had major 2 findings. First, initial LVDD was significantly smaller in patients with LVRR than in those without. Second, when patients were further allocated according to initial LV end-diastolic dimension ≤ 63.5 mm with atrial fibrillation, the combined parameter was a significant predictor of LVRR by univariate logistic regression analysis (odds ratio: 5.78, p = 0.030) (revised manuscript, page 9, line 14- page 10, line 1). I have referred the paper in the revised manuscript (Ref # 11). I have not referred the paper by Merlo et al. (J Am Coll Cardiol
2011;57:1468-76), because 35% (85/242) of the study patients were on beta blockers.

5. The correlation between atrial fibrillation and LVRR was not statistically significant in the present study ("The prevalence of atrial fibrillation tended to be higher in patients with LVRR than in those without, 40% vs. 14%, \( p = 0.067 \)) and the pathophysiological scenario proposed by the authors as an explanation for their finding is not very convincing. A higher sample size would be needed to clarify this issue.

According to the referee’s suggestion, I have deleted “The prevalence of atrial fibrillation tended to be higher (40% vs. 14%, \( p = 0.067 \))” and “The presence of atrial fibrillation tended to be associated with LVRR (sensitivity: 40%, specificity: 86%, \( p = 0.067 \)).” in the all sections of my manuscript and focus the discussion and conclusions only on the variables significantly different between the 2 studied group. I have corrected the identical sentences in Abstract, as follows: The presence of atrial fibrillation was 40% in patients with LVRR and 14% in those without (\( p = 0.067 \)) (revised manuscript, page 2, line 10-11). I have added the identical sentences in Discussion, as follows: Although these results indicate that patients of the present study with atrial fibrillation had IDC but not tachycardia-induced cardiomyopathy, initial LV end-diastolic dimension ≤ 63.5 mm with atrial fibrillation was a significant predictor of LVRR, suggesting that atrial fibrillation might be associated with future LVRR (revised manuscript, page 12, line 1-4). I have also corrected the identical sentences in Discussion, as follows: Further studies with a large number of patients are required to confirm the results of the present study (revised manuscript, page 13, line 2-3).