

# Effects of erythropoietin administration on mitral regurgitation and left ventricular remodeling in heart failure patients

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## Abstract

The effects of erythropoietin administration on mitral regurgitation in patients with congestive heart failure have not yet been examined. After 2 months, erythropoietin treatment results in a significant reduction in left ventricular volumes and mitral regurgitation severity and improves hemodynamics.

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Anemia and mitral regurgitation (MR) are frequent in patients with congestive heart failure (CHF) [1]. Both promote left ventricular (LV) remodeling resulting in an increased morbidity and mortality [2]. The effects of erythropoietin (EPO) on left ventricular (LV) remodeling, MR, and indices of LV filling pressure have not yet been examined. We prospectively included 28 consecutive outpatients presenting with severe CHF due to systolic LV dysfunction (ejection fraction <45%), anemia (hemoglobin <12 g/dl), and chronic renal failure (creatinine clearance <45 ml/min). All were in a pre-dialysis condition. Fourteen of them were randomly assigned to receive EPO therapy and the remaining 14 served as control patients. Echocardiography was performed at baseline and after 2 months of treatment. Age, gender, medical history and treatment regimen were distributed similarly in both groups. After 2 months of EPO treatment, the New York Heart Association class improved ( $2.2 \pm 0.5$  vs  $3.4 \pm 0.5$ ,  $p < 0.01$ ) whereas no significant change was observed in the control group. The hemoglobin level ( $13.1 \pm 0.4$  vs  $10.1 \pm 0.3$  g/dl,  $p < 0.001$ ) as well as the systolic blood pressure also increased in the treated group. The EPO treatment was accompanied by a significant decrease in LV end-diastolic and

end-systolic volumes, in ERO — degree of MR —, and in  $E/Em$  whereas LV ejection fraction and the LV systolic performance as estimated by LV  $dP/dt$  improved ( $p < 0.001$ ). The LV function, LV volumes, and MR degree remained fairly unchanged in the control group. At baseline, higher LV volumes, larger mitral annular areas and greater apical displacement of posterior papillary muscle ( $r = 0.67$ ,  $p = 0.0037$ ) were associated with higher ERO. Mitral deformation increased significantly with higher degree of MR. LV  $dP/dt$  was not related to ERO. EPO-induced changes in MR were unrelated to changes in LV volumes whereas they were correlated with changes in systolic blood pressure, in valvular deformation and in regional LV remodeling. The strongest correlations with ERO changes were observed with the differences in apical displacement of posterior papillary muscle, in LV  $dP/dt$  and in coaptation height. Using multivariate analysis, a decrease in the apical displacement of posterior papillary muscle ( $p = 0.0004$ ) and the rise in LV  $dP/dt$  ( $p = 0.001$ ) emerged as independent cofactors associated with EPO-induced MR reduction ( $R^2 = 0.91$ ). To note, the decrease in LV filling pressure —  $E/Em$  — was correlated with changes in ERO and with the decrease in transtricuspid pressure gradient.

Anemia, increased LV filling pressure, LV remodeling and MR are frequent in CHF patients [1]. All of these features are independently predictive of adverse outcome. The present study shows that treating anemia by EPO in CHF results in a significant reduction in LV volumes and MR severity and improves hemodynamics. Decrease in MR

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degree is interrelated to changes in regional LV remodeling and is directly correlated to the improvement in LV systolic performance. MR improvement is accompanied by both a decrease in  $E/Em$  ratio — a non-invasive estimate of LV filling pressure — and in pulmonary pressure.

The present study confirms and extends the results of previous reports showing that EPO administration improves clinical status and hemodynamics and is accompanied by progressive reverse LV remodeling [3,4]. As a result, the LV ejection fraction increases and the LV systolic performance — LV  $dP/dt$  — rises. Concomitantly, the tension applied on mitral valve decreases — reverse regional LV remodeling (slighter apical displacement of mitral leaflets). The balance of forces acting on mitral leaflets is thus improved resulting in a significant decrease in MR severity. Under basal conditions, regurgitant volume is also determined by the systolic pressure gradient across the orifice [5]. Transmitral pressure, which drives regurgitant flow, also promotes valve closure. Therefore, the rise in systemic blood pressure observed in the EPO group could also reduce MR by increasing closing force. Obviously, this positive effect is only possible if tethering decreased. Transmitral pressure can also be increased by decreasing atrial pressure which reflects the level of LV end-diastolic pressure. In this study, we showed that LV filling pressure as estimated by  $E/Em$  was lower after EPO treatment. Such a reduction reflects the decrease in MR degree and better LV diastolic function.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [6].

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