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The association of functional mitral regurgitation and anemia in patients with non-ischemic dilated cardiomyopathy

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Abstract

Background: *We investigated the association between anemia and functional mitral regurgitation (MR) in non-ischemic dilated cardiomyopathy (DCM) patients with sinus rhythm and normal renal function.*

Methods: *Sixty non-ischemic DCM patients with sinus rhythm and left ventricular ejection fraction < 40% were recruited. Functional MR was quantified with the proximal isovelocity surface area method. MR was graded according to the mitral regurgitant volume (Reg Vol) or effective regurgitant orifice (ERO) area. The clinical, biochemical and echocardiographic correlates of functional MR severity were investigated in patients with DCM.*

Results: *Hemoglobin degrees were significantly different between various MR levels (mild MR 13.9 ± 1.7 mg/dL, moderate MR 12.3 ± 1.5 mg/dL, moderate to severe MR 10.8 ± 0.9 mg/dL). Receiver operating characteristic (ROC) analysis was performed to assess the utility of hemoglobin levels to predict moderate or severe functional MR. A hemoglobin level less than 12.5 mg/dL predicted moderate or high MR with 80% sensitivity and 58% specificity (AUC: 0.789, 95% CI: 0.676–0.901, p < 0.0001). Logistic regression analysis was performed to determine the independent predictors of moderate or severe levels of MR. The left atrium diameter (OR: 19.3, 95% CI: 1.4–27.1, p = 0.028) and presence of anemia (OR: 11.9, 95% CI: 1.22–42.5, p = 0.0045) were independent predictors of moderate or severe functional MR.*

Conclusions: *The presence of anemia and enlarged left atrium are independent predictors of moderate or severe functional MR in non-ischemic DCM patients with normal renal function. Hemoglobin levels less than 12.5 mg/dL should alert the physician for the presence of moderate or severe MR in patients with DCM.* (Cardiol J 2010; 17, 3: 274–280)

Key words: anemia, functional mitral regurgitation, dilated cardiomyopathy

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Introduction

Recent studies have revealed that patients with chronic heart failure (CHF) are frequently anemic, and that anemia is associated with increased mortality and morbidity in these patients [1–4]. Ezekowitz et al. [1] demonstrated that anemia was present in 17% of more than 12,000 heart failure patients and associated with a hazard ratio of 1.34 for mortality. Functional mitral regurgitation (MR) is another adverse prognostic factor in patients with dilated cardiomyopathy (DCM) [5, 6]. Blondheim et al. [5] reported that the presence of MR is a sensitive marker of decreased survival. They reported a significant difference in survival (22% *vs* 60% at 32 months, $p < 0.005$) in DCM patients with and without MR. However, the association between anemia and functional MR is unclear in DCM. In our study, we investigated the relation between hemoglobin levels and functional MR in non-ischemic DCM patients with sinus rhythm and normal renal functions.

Methods

The study population was selected from patients evaluated in Kartal Kosuyolu Heart Education and Research Hospital cardiology outpatient clinic between January 2007 and March 2009. All patients who met the inclusion criteria (presence of heart failure symptoms, left ventricular ejection fraction < 40%, sinus rhythm, a coronary angiogram establishing the non-ischemic origin of heart failure that was performed within the last six months) were asked to participate in the study and those who accepted were enrolled consecutively in this cross-sectional study. Following the recruitment period, the study population included 60 non-ischemic DCM patients.

The local ethics committee approved this cross-sectional study.

Patients with organic heart valve diseases that may cause mitral regurgitation (rheumatic or degenerative heart valve disease, mitral annular calcification, mitral valve prolapsus, chordae tendinea rupture), history of acute coronary syndrome, ischemic electrocardiographic (ECG) findings, significant coronary artery disease in coronary angiography (> 50% luminal stenosis), permanent pacemakers, and chronic kidney disease (> stage 3 kidney disease) were excluded from the study. All patients were evaluated carefully for their functional capacities. 12-lead ECGs were obtained (0.5 to 150 Hz, 25 mm/s, 10 mm/mV). Blood samples for N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, hemoglobin, hematocrit, blood erythrocyte count, and creatinine levels were obtained following a resting period after the echocardiographic examinations. Patients were categorized into two groups according to their QRS interval time (< 120 ms, ≥ 120 ms). The World Health Organization definition of anemia (hemoglobin concentration 13.0 g/dL in men and 12.0 g/dL in women) was used in the classification of patients with or without anemia [7].

Echocardiographic examinations

Standard echocardiographic evaluations with Doppler study were performed (System 5, Vingmed-General Electric, Horten, Norway). Left ventricle (LV) dimensions and ejection fractions were measured by modified biplane Simpson's method according to the guidelines of the American Society of Echocardiography [8]. The quantification of functional mitral regurgitation was performed by using the proximal isovelocity surface area method as previously described [9]. The effective regurgitation orifice (ERO) area [cm^2] and the regurgitatnt volume (Reg Vol) [mL] were used as variables expressing the severity of MR. The maximal rate of left ventricular systolic pressure increase (LV dP/dt) was used as an index of LV systolic performance and estimated from the steepest increasing segment of the continuous wave Doppler MR velocity spectrum [10]. Pulmonary artery systolic pressure was estimated from the tricuspid regurgitation jet by continuous wave Doppler. Patients were subdivided into four groups based on their Reg Vol or ERO (mild MR: Reg Vol < 20 mL/beat or ERO < 0.20 cm^2, moderate MR: Reg Vol = 20––39 mL/beat or ERO = 0.20–0.29 cm^2, moderate to severe MR: Reg Vol = 40–59 mL/beat or ERO = = 0.30–0.39 cm^2, severe MR: Reg Vol > 60 mL/beat or ERO > 0.40 cm^2) and the clinical, biochemical, and echocardiographic correlates of functional MR degree in patients with DCM were investigated.

Tissue Doppler imaging (TDI) was performed in the apical views (four chamber and long axis) for the long axis motion of the LV and tricuspid annulus with a 2.5 MHz phase array transducer as previously described [11, 12]. For detailed assessment of regional myocardial function, the sampling window was placed at the myocardial segment of interest. In the apical four-chamber view, left ventricular septal and lateral wall and lateral tricuspid annulus were assessed. Myocardial sustained systolic (s), early diastolic (e), and late diastolic (a) velocities from the basal septal and tricuspid annulus were calculated.

NT-proBNP levels

Plasma NT-proBNP levels were obtained after a 20 minute rest following the echocardiographic evaluation. All of the blood samples were drawn from the antecubital vein. Samples were kept in vacutainers with EDTA, and centrifuged for 5 min at 1500 rpm. Separated plasma samples were kept at –80°C until the analysis date. Commercial NT-proBNP assays (Elecsys, Roche Diagnostics Corporation, Indianapolis, Indiana, USA) were used for measurements.

Statistical analysis

Statistical analysis was performed using a statistical software program (SPSS for Windows, version 13.0; SPSS Inc, Chicago, Illinois, USA). Data are presented as mean ± standard deviation, controlled for normal distribution by Kolmogorov-Smirnov test and compared using unpaired student t-test when normally distributed. Nonparametric tests were also applied in non-normal distributions (Mann-Whitney U test). Categorical differences between two groups were compared by the Pearson χ^2 test. The difference in hemoglobin levels between various degrees of MR was evaluated by analysis of variance (ANOVA) test. Hemoglobin levels were evaluated by receiver operating characteristics (ROC) analysis in predicting functional MR. In order to determine the optimal hemoglobin value in predicting moderate or higher levels of MR, the closest value to the best specificity and sensitivity point on the ROC curve was identified. Logistic regression analysis was used to identify the independent predictors of moderate or higher levels of MR out of the clinical, ECG, and echocardiographic parameters. A probability value of $p < 0.05$ was considered as significant.

Results

The study population included 22 women (37%) and 38 men (63%). Mean age was 43 ± 15. Twenty-three patients (38%) were anemic. Anemic patients had larger left atrial diameters ($p = 0.012$), greater mitral Reg Vol ($p < 0.0001$) and ERO areas ($p < 0.0001$), shorter E wave deceleration ($p = = 0.026$) and isovolumic relaxation times ($p = 0.007$), and lower TDI derived tricuspid annulus peak systolic velocities (RVs; $p = 0.002$) compared to non-anemic patients. Eight of the 23 patients were in NYHA functional class III–IV in the anemic group; five out of 37 patients in the non-anemic group were in NYHA functional class III–IV (Pearson χ^2: 3.78, $p = 0.048$). The remaining clinical, electrocardiographic, biochemical and echocardiographic parameters were similar between the two groups. The characteristics of patients with and without anemia are reported in Table 1.

The difference in hemoglobin levels in patients with various degrees of MR was evaluated by ANOVA. Thirty-six patients (60%) had mild, 20 patients (33.3%) had moderate, and four (6.6%) patients had moderate to severe MR. There was no patient with severe MR. The hemoglobin levels were significantly different between various MR levels (mild MR; 13.9 ± 1.7 mg/dL, moderate MR; 12.3 ± 1.5 mg/dL, moderate to severe MR; 10.8 ± ± 0.9 mg/dL; $p = 0.001$ for mild and moderate MR, $p = 0.001$ for mild and moderate to severe MR, $p = 0.062$ for moderate and moderate to severe MR). Significant correlations between Reg Vol, echocardiographic and biochemical parameters are reported in Table 2.

The study group was categorized into two subgroups according to the MR severity which was determined by the Reg Vol 20 mL/beat or ERO area 0.20 cm^2. Patients with mild MR constituted Group I ($n = 36$) and those with higher degrees of MR Group II ($n = 24$). The patients in Group II had larger left atrial ($p < 0.0001$), left ventricular end-systolic ($p < 0.0001$), end-diastolic dimensions ($p = 0.001$), and lower left ventricular ejection fraction ($p = = 0.027$), septum TDI peak systolic velocity (Sep TDIs) ($p = 0.008$), and RVs ($p = 0.023$) than the patients in Group I. Mitral E wave velocity ($p < 0.0001$) and E/A ratio ($p = 0.002$) were elevated, E wave deceleration ($p < 0.0001$) and isovolumic relaxation times ($p < 0.0001$) were shorter, hemoglobin ($p < 0.0001$) and hematocrit ($p = 0.002$) levels were lower in Group II patients. Four of 36 patients (11%) in Group I and nine of 24 patients (37.5%) in Group II were in NYHA functional class III–IV (Pearson χ^2: 5.9, $p = 0.015$). Eight of 36 patients (22%) in Group I and 15 of 24 patients (62.5%) in Group II were anemic (Pearson χ^2: 9.88, $p = 0.002$). Characteristics of the patients in Group I and Group II are reported in Table 3.

ROC analysis was performed to assess the utility of hemoglobin to predict moderate or severe levels of functional MR. A hemoglobin level less than 12.5 mg/dL predicted moderate or higher MR with 80% sensitivity and 58% specificity (AUC: 0.789, 95% CI: 0.67–0.90, $p < 0.0001$) (Fig. 1). Logistic regression analysis was also performed to evaluate the independent predictors of moderate or severe levels of MR. NYHA functional class (class I–II *vs* class III–IV), plasma NT-proBNP levels, left ventricular ejection fraction, left atrium diameter, left ventricu-

Table 1. Characteristics of non-ischemic dilated cardiomyopathy patients with and without anemia.

	Anemia (+); n = 23	Anemia (–); n = 37	P
Gender (female/male)	8 (35%)/15 (65%)	14 (38%)/23 (62%)	0.811
Age (years)	40±16	44±14	0.394
NYHA class I–II/III–IV	**15 (65%)/8 (35%)**	**32 (86%)/5 (14%)**	**0.048**
QRS duration (< 120/≥ 120)	17 (74%)/6 (26%)	25 (68%)/12 (32%)	0.555
Log NT-proBNP	3.14±0.5	2.92±0.6	0.225
Hemoglobin	**11.4±1.1**	**14.3±1.3**	**< 0.0001**
Hematocrit	**34.4±3.2**	**41.8±4.1**	**< 0.0001**
LA [cm]	**4.9±0.9**	**4.3±0.7**	**0.012**
LVEDD [cm]	7.1±0.9	6.7±0.8	0.094
LVESD [cm]	6.2±0.8	5.8±0.8	0.067
LVEF (%)	28.1±9	30.4±6	0.297
dP/dt [mm Hg/ms]	524±149	572±148	0.252
Mitral Reg Vol [mL]	**29±13**	**16±8**	**< 0.0001**
ERO [cm^2]	**0.22±0.12**	**0.12±0.07**	**< 0.0001**
Mitral E vel. [m/s]	0.97±0.31	0.82±0.27	0.089
Mitral A vel. [m/s]	0.53±0.20	0.60±0.24	0.285
E/A	2.14±1.1	1.67±0.9	0.130
EDT [ms]	**128±56**	**170±71**	**0.026**
IVRT [ms]	**87±32**	**114±26**	**0.007**
RV TDI s [cm/s]	**7.4±2.7**	**9.5±2.1**	**0.002**
Sep TDI s [cm/s]	3.1±1.4	3.5±1.1	0.061
Sep TDI e [cm/s]	3.5±1.9	3.7±1.9	0.655
Sep TDI a [cm/s]	3.8±2.0	4.3±1.7	0.316
E/e'	38.8±29	28.6±17	0.103

dP/dT — delta pressure/delta time; EDT — E wave deceleration time; ERO — effective regurgitant orifice area; IVRT — isovolumic relaxation time; LA — left atrium diameter; LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; LVESD — left ventricular end--systolic diameter; NYHA — New York Heart Association; Reg Vol — regurgitant volume; RV TDI s — tricuspid annulus TDI peak systolic velocity; Sep TDI a — basal septum TDI late diastolic velocity; Sep TDI e — basal septum TDI early diastolic velocity; Sep TDI s — basal septum TDI peak systolic velocity

Table 2. Correlations between mitral regurgitant volume and echocardiographic and biochemical parameters.

	R	P
ERO area [mm^2]	0.850	< 0.0001
Log NT-proBNP	0.407	0.003
NYHA class I–II/III–IV	0.351	0.006
LA [cm]	0.554	< 0.0001
LVEDD [cm]	0.412	0.001
LVESD [cm]	0.467	< 0.0001
LVEF (%)	–0.306	0.017
E/A	0.402	0.007
PAP [mm Hg]	0.398	0.02
RV TDI s [cm/s]	–0.405	0.001
Sep TDI s [cm/s]	–0.350	0.007
Hemoglobin [mg/dL]	–0.551	< 0.0001
Hematocrit (%)	–0.457	< 0.0001

ERO — effective regurgitant orifice area; NYHA — New York Heart Association; LA — left atrium diameter; LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end systolic diameter; LVEF — left ventricular ejection fraction; PAP — pulmonary artery systolic pressure,;RV TDI s — tricuspid annulus TDI peak systolic velocity; Sep TDI s — basal septum TDI peak systolic velocity

lar end-systolic and end-diastolic dimensions, E/A ratio, Sep TDIs, RVs and anemia (presence of anemia or not) were the covariates and included in the model. Logistic regression analysis revealed left atrial diameter (OR: 19.3, 95% CI: 1.4–27.1, p = 0.028), and the presence of anemia (OR: 11.9, 95% CI: 1.22––42.5, p = 0.0045) were the independent predictors of moderate or higher levels of functional MR.

Discussion

Our study indicates that non-ischemic DCM patients with anemia have higher degrees of functional MR and enlarged left atria. In addition, these patients had impaired tissue Doppler derived right ventricular systolic function. Patients with higher NYHA functional class were also more prevalent in this group. Hemoglobin levels less than 12.5 mg/dL indentified the non-ischemic DCM patients with moderate or higher degrees of functional MR.

The estimated prevalence of anemia in patients with CHF ranges from 4% to 61% (median 18%).

Table 3. Characteristics of non-ischemic dilated cardiomyopathy patients with mild and moderate or higher levels of functional mitral regurgitation (MR).

	Group I; n = 36 MR volume < 20 mL	Group II; n = 24 MR volume ≥ 20 mL	P
Gender (female/male)	14 (39%)/22 (61%)	8 (33%)/16 (67%)	0.662
Age (years)	44 ± 15	40 ± 16	0.252
NYHA class I–II/III–IV	**32 (89%)/4 (11%)**	**15 (62%)/9 (38%)**	**0.015**
QRS duration (< 120/≥ 120)	26 (72%)/10 (28%)	15 (62%)/9 (38%)	0.334
Log NT-proBNP	2.88 ± 0.6	3.22 ± 0.5	0.052
Hemoglobin	**13.9 ± 1.7**	**12.1 ± 1.5**	**< 0.0001**
Hematocrit	**40.6 ± 5.1**	**36.4 ± 4.3**	**0.002**
LA [cm]	**4.2 ± 0.6**	**5.0 ± 0.8**	**< 0.0001**
LVEDD [cm]	**6.6 ± 0.8**	**7.3 ± 0.7**	**0.001**
LVESD [cm]	**5.6 ± 0.8**	**6.4 ± 0.6**	**< 0.0001**
LVEF (%)	**31.1 ± 7**	**27.1 ± 7**	**0.027**
dP/dt [mm Hg/ms]	592 ± 149	496 ± 131	0.014
Mitral Reg Vol [mL]	**12.5 ± 4.1**	**33.6 ± 9.3**	**< 0.0001**
ERO [cm^2]	**0.09 ± 0.03**	**0.25 ± 0.11**	**< 0.0001**
Mitral E vel. [m/s]	**0.75 ± 0.25**	**1.07 ± 0.24**	**< 0.0001**
Mitral A vel. [m/s]	0.62 ± 0.24	0.50 ± 0.19	0.052
E/A	**1.52 ± 1**	**2.40 ± 0.8**	**0.002**
EDT [ms]	**180 ± 72**	**114 ± 36**	**< 0.0001**
IVRT [ms]	**116 ± 26**	**85 ± 29**	**< 0.0001**
RV TDI s [cm/s]	**9.3 ± 2.2**	**7.8 ± 2.8**	**0.023**
Sep TDI s [cm/s]	**3.7 ± 1.2**	**2.8 ± 1.0**	**0.008**
Sep TDI e [cm/s]	3.6 ± 2.0	3.7 ± 1.8	0.891
Sep TDI a [cm/s]	4.4 ± 1.8	3.6 ± 1.8	0.081
E/e'	**30 ± 26**	**35 ± 14**	**0.478**

dP/dT — delta pressure/delta time; EDT — E wave deceleration time; ERO — effective regurgitant orifice area; IVRT — isovolumic relaxation time; LA — left atrium diameter; LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; LVESD — left ventricular end--systolic diameter; NYHA — New York Heart Association; Reg Vol — regurgitant volume; RV TDI s — tricuspid annulus TDI peak systolic velocity; Sep TDI a — basal septum TDI late diastolic velocity; Sep TDI e — basal septum TDI early diastolic velocity; Sep TDI s — basal septum TDI peak systolic velocity

The prevalence of anemia is increased in CHF populations with comorbid kidney disease, advanced age, and more severe heart failure symptoms [13]. Anemia was found to be an independent predictor of high mortality and poor clinical outcomes in patients with advanced heart failure [2, 4, 14]. It is unclear whether anemia worsens heart failure or it is just a marker of more severe underlying myocardial disease. Anemia can also be a marker of more severe underlying myocardial disease.

On the other hand, the presence of functional MR is also considered to be a risk factor for poor clinical outcome in DCM [5, 15]. Functional MR is associated with poor NYHA functional class, lower left ventricular ejection fraction, higher left ventricular end-diastolic and right sided pressures in patients with DCM [15]. Functional MR results in more left ventricular dilatation, and aggravates the hemodynamic decompensation. In patients with moderate to severe MR, anemia may be an additional contributing factor to hemodynamic and functional decompensation and poor clinical outcome in non--ischemic DCM patients. In addition, right ventricular systolic performance is an important predictor of morbidity and mortality in ischemic and non-ischemic DCM [16–18]. Patients with left ventricular end-diastolic diameter > 70 mm and RVs < 10.8 cm/s are the highest risk heart failure group independent from the etiology. This condition is even more peculiar in patients with DCM [16]. We found that tissue Doppler derived right ventricular systolic function was significantly impaired in anemic DCM patients in our study.

Although there are controversies about the effect of anemia on poor left ventricular function and severely limited exercise capacity [19–21], medical management of anemia has been demonstrated to improve functional capacity and quality of life in

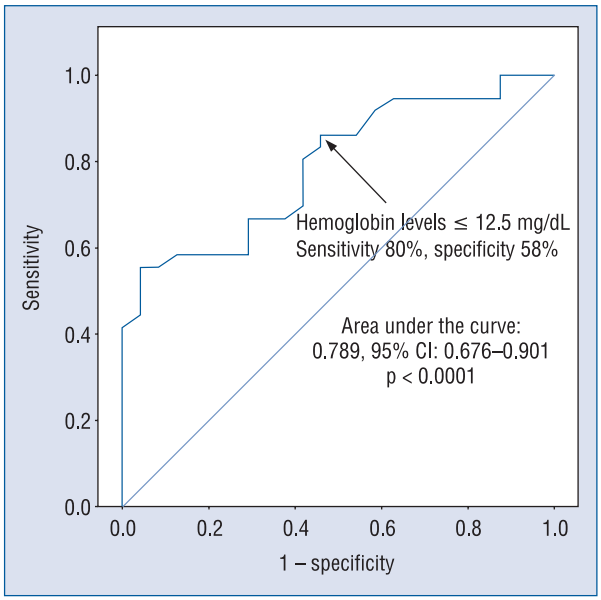

Figure 1. Receiver operating characteristics (ROC) curve demonstrating the utility of anemia to predict functional mitral regurgitation (MR). Hemoglobin level less than 12.5 mg/dL predicts moderate or higher levels of functional MR with 80% sensitivity and 58% specificity.

patients with heart failure [22]. Prediction of moderate or severe functional MR with high sensitivity and specificity by considering anemia in advance may be useful in the routine practice. We suggest that the presence of anemia should alert the physician to the presence of moderate or higher levels of MR in DCM patients. Enlarged left atrial dimensions, increased mitral Reg Vol, shorter E wave deceleration and isovolumic relaxation times and lower RVs in anemic patients suggest that anemia is a marker of more severe underlying myocardial disease in non-ischemic DCM patients.

Chronic renal disease is common in patients with heart failure and their prognosis is usually poor [23]. Among heart failure patients, anemia is more common in patients with chronic kidney disease and has been found to independently confer a two-fold higher risk of death [24]. In our study, patients with chronic renal failure were excluded in order to evaluate the association between anemia per se and echocardiographic parameters. In our study, anemia was associated with increased mitral Reg Vol and impaired right ventricular functions in DCM patients, despite normal kidney function.

The small study population may be a major limitation. Therefore, our findings need confirmation by larger studies to increase the significance and clinical accuracy of our results. Whether treatment of anemia may influence the functional status, morbidity, mortality, and functional MR of non-ischemic DCM needs further prospective studies.

Conclusions

The presence of anemia independently predicts moderate or severe levels of functional MR in non-ischemic DCM patients with normal kidney functions. Hemoglobin levels less than 12.5 mg/dL should alert the physician for a moderate or severe MR in patients with non-ischemic DCM.

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