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The Impact of Beta-blockade on Right Ventricular Function in Mitral Regurgitation



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Background

Although mitral regurgitation (MR) results in left ventricular (LV) volume overload, right ventricular (RV) function may also be impaired. We investigated the influence of short-term beta-blockade on RV function in patients with moderate-severe MR.

Methods

Twenty-six patients were randomised in a cross-over design to receive two weeks of beta-blockade or placebo. Echocardiography was performed at baseline and at the end of the treatment periods. Measurements included: RV ejection fraction (RVEF) tricuspid annular motion and Tei index.

Results

No differences in mean RVEF (64.0 ± 6.0 v $67.0 \pm 8.0\%$, $p = 0.3$), tricuspid annular motion (13.5 ± 3.0 v 14.7 ± 2.9 cm/s, $p = 0.5$), or median Tei index (0.61 ($0.54, 0.88$) v 0.59 ($0.54, 0.74$), $p = 0.8$) were observed between placebo and metoprolol, despite significantly longer cardiac time intervals. Tei index under both conditions was significantly reduced.

Conclusions

Short-term treatment with a beta-blocker did not influence RV function in these patients. Interestingly, the RV Tei index was high suggesting significant RV dysfunction despite normal RVEF.

Keywords

Mitral regurgitation • Beta-blockers • Tei index • Echocardiography • Doppler

Introduction

Degenerative mitral regurgitation (MR) results in left ventricular (LV) volume overload and LV dysfunction that contributes to prognosis [1]. RV function is also prognostically important [2]: tricuspid annular plane systolic excursion (TAPSE), a measure of systolic annular descent, is correlated with RV ejection fraction (RVEF) [3] and predicts survival after mitral valve repair [4].

In patients with LV systolic dysfunction, beta-blockade improves prognosis [5] and reverses adverse LV remodelling [6], potentially mediated through a long-term reduction in myocyte strain, also seen with MR-related chronic LV

volume overload [7]. Recently, we reported that short-term beta-blocker treatment did not change MR volume but decreased LV work in patients with moderate-severe MR [8]. The aim of this study was to investigate the influence of short-term beta-blocker on RV.

Patients and Methods

The methods have been reported elsewhere [8]. Briefly, patients with moderate-severe MR, normal LV systolic function (echo LV ejection fraction >55%) and sinus rhythm were recruited into this double-blind, randomised, crossover

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design trial which had two treatment periods (14 ± 3 days) with a two to four days washout between treatments. Subjects were randomised to extended-release metoprolol or placebo or vice versa. The initial dose was one continuous-release metoprolol tablet (47.5 mg) or placebo per day. The dose was increased every three to four days if the patient had no side effects, resting heart rate was ≥ 60 bpm, and systolic blood pressure was ≥ 110 mm Hg, with a maximum dose of 190 mg/d. The dose was reduced if clinically indicated. All other medication was unchanged throughout. At baseline, and the end of each study period, clinical examination, ECG, and echocardiography were completed. Echocardiographic measurements were performed blind: RVEF (area-length method, apical four-chamber view); 2D TAPSE; pulsed-wave tissue Doppler imaging (TDI) of longitudinal RV free wall annular motion (systolic (Sm), early diastolic (Em), late diastolic (Am) velocities); Tei index (Tei index = (isovolumetric contraction time + isovolumic relaxation time)/ejection time). Similar measurements were obtained from the LV by both conventional and tissue Doppler (septal and lateral walls) methods. From the TDI recordings, the time interval from the end of one to the onset of the next tricuspid annular velocity pattern during diastole (a) was measured. The duration of the Sm (b) was measured from the onset to the end of the Sm. The Tei index was calculated as $(a - b)/b$. Very few patients had sufficient tricuspid regurgitation to allow measurement of RV systolic pressure.

Statistical Analysis

Continuous variables were compared by treatment arm using paired Student *t*-tests (Wilcoxon for non-parametric data). Pearson correlation coefficients are reported, with a value of $p < 0.05$ was considered statistically significant.

Results

Twenty-six patients were enrolled: mean age 61 ± 10 years; seven patients had mild dyspnoea on exertion (NYHA class IIa); 12 reported a history of treated hypertension. Most patients had posterior mitral leaflet prolapse (Table 1). Heart rate was significantly lower on metoprolol (65 ± 10 bpm) compared to placebo (55 ± 7 bpm), but no significant changes in RV volumes or function were observed (Table 2). Tei index was similar on metoprolol and placebo, despite there being a significantly longer *a* time (519 v 476 , $p = 0.005$) and a trend towards longer *b* time (309 v 299 , $p = 0.07$). Similar results were observed for LV Tei index (Table 2). Tei index under both conditions was significantly different to the published normal values for RV Tei index (0.28 ± 0.04 by conventional Doppler [9] and 0.43 ± 0.07 [10]). We have previously reported no impact on LV volumes and EF [8] but this study confirmed similar stable results for LV parameters and also elevated LV Tei index (Table 2). The LV Tei index values are significantly different to the published normal values (0.33 ± 0.09 by conventional Doppler and 0.42 ± 0.09 by TDI [11]).

Table 1 Demographic and Clinical Characteristics of the Study Population.

Characteristic	Whole group (N = 26)
Age, years	61 ± 10
Male, <i>n</i> (%)	21 (84)
Ethnic group, <i>n</i> (%)	
White	20 (80)
Maori/Pacific Islander	3 (12)
Other	2 (8)
Body mass index, kg/m ²	25.8 ± 3.8
History of hypertension, <i>n</i> (%)	12 (48)
Medical treatment during study	
ACE inhibitor, <i>n</i> (%)	11 (44)
Loop diuretic, <i>n</i> (%)	1 (4)
Symptoms	
Asymptomatic, <i>n</i> (%)	19 (73)
NYHA class a symptoms, <i>n</i> (%)	7 (28)
Leaflet prolapse	
Anterior leaflet, <i>n</i> (%)	2 (8)
Posterior leaflet, <i>n</i> (%)	14 (56)
Bileaflet, <i>n</i> (%)	9 (36)
Flail or partial flail mitral leaflet, <i>n</i> (%)	11 (44)
Echocardiography	
LV end-systolic volume, mL	81 ± 21
LV end-diastolic volume, mL	229 ± 50
LV ejection fraction, %	65 ± 5
Mitral regurgitant volume, mL	59 ± 36

Data are mean \pm SD or number (percentage).

Abbreviations: ACE, angiotensin-converting enzyme; NYHA, New York Heart Association.

Discussion

We have demonstrated that RV function in patients with MR is not influenced by short-term beta-blocker treatment. However, the RV Tei indices were substantially higher than reported normal values [9], suggesting significant RV dysfunction despite normal RVEF. Thus, the Tei index, a measure of global cardiac function [9], might be a more sensitive parameter to estimate the RV dysfunction. Similar results were observed for the LV Tei index.

This was a small study, possibly underpowered that is mostly hypothesis generating. We have used some published normal values for RV Tei and it is acknowledged that including our own control group would have been optimal. Future work should validate the Tei index measured from Tissue Doppler in this setting against a control series, should include more complex assessment of systolic time intervals, and ideally should include 3D echo and global longitudinal strain.

Early detection of ventricular dysfunction is crucial in the setting of severe MR: by the time LV dysfunction is apparent using conventional echocardiography it is often irreversible.

Table 2 Effects of Metoprolol on Heart Rate and Ventricular Function.

	Placebo (N = 26)	Metoprolol (N = 26)	p value
Heart rate, bpm	65 ± 10	55 ± 7	<0.0001
RV end-systolic volume, mL	19.1 ± 7.5	18.3 ± 8.3	0.7
RV end-diastolic volume, mL	52.9 ± 18.9	55.8 ± 18.1	0.5
RV ejection fraction, %	64.0 ± 6.0	67.0 ± 8.0	0.3
RV TAPSE, cm	2.57 ± 0.34	2.63 ± 0.40	0.9
Tricuspid systolic annular velocity, cm/s	13.5 ± 3.0	14.7 ± 2.9	0.5
TDI RV Em/Am	0.87 (0.75–1.43)	0.81 (0.65–1.13)	0.97
TDI RV time a, ms	476 (443–493)	519 (492–535)	0.005
TDI RV time b, ms	299 (262–312)	309 (293–339)	0.07
TDI RV Tei index	0.61 (0.54–0.88)	0.59 (0.54–0.74)	0.8
Left ventricular Tei measurements			
Mitral LV time a, ms	432.7 ± 48.0	455.8 ± 53.5	0.003
Mitral LV time b, ms	261.6 ± 32.5	271.6 ± 36.2	0.009
Mitral LV Tei index	0.68 (0.58–0.81)	0.61 (0.52–0.80)	0.59
TDI (lateral) LV time a, ms	446.3 ± 60.7	506.4 ± 50.6	0.005
TDI (lateral) LV time b, ms	275.5 ± 46.8	299.3 ± 39.9	0.003
TDI (lateral) LV Tei index	0.64 (0.57–0.84)	0.67 (0.57–0.78)	0.97
TDI (septal) LV time a, ms	477.8 ± 54.3	494.8 ± 52.5	0.115
TDI (septal) LV time b, ms	295.9 ± 34.6	314.5 ± 34.7	0.007
TDI (septal) LV Tei index	0.62 (0.57–0.69)	0.56 (0.50–0.67)	0.19

Abbreviations: a, the time interval from the end of one to the onset of the next tricuspid annular velocity pattern during diastole; b, duration of systole using systolic annular velocity; Am, late mitral annular velocity; Em, early mitral annular velocity; LV, left ventricle; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; Data are mean ± standard deviation or median (95% confidence interval).

However, if more objective measures of both RV and LV systolic dysfunction were available, perhaps a more precise management might be obtainable.

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