Effectiveness of treatment with ivabradine on clinical and instrumental endpoints in patients with Duchenne Muscular Dystrophy

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Background

Increased survival in Duchenne Muscular Dystrophy (DMD) is due to an improvement in clinical care of the musculoskeletal and respiratory systems and has led to an increased incidence of dilated cardiomyopathy (DCM). Cardiac-related deaths are now seen in approximately 20% of DMD patients. The treatment for the cardiovascular complications contemplates the association of ACE inhibitors and Beta-blockers, which showed to improve the survival rate in both symptomatic and asymptomatic patients[1, 2]. The effects of ivabradine treatment in this population has not yet been investigated.

Ivabradine inhibits the hyperpolarization-activated pacemaker (If) current in the sino-atrial node and provides pure heart rate (HR) reduction without effects on other hemodynamic parameters [3] (fig.1). HR reduction mediated by ivabradine demonstrated also an improvement of total arterial compliance, a reduction of the arterial elastance and, as a consequence, an increasing of the stroke volume in patient with heart failure (HF) [4].

Sargento et al. recently demonstrated a significative reduction of NT-proBNP levels in a short term Ivabradine treatment closely correlated with HR reduction [5].

Nevertheless Ivabradine demonstrated positive effects on LV remodeling and function independently from HR reduction, suggesting the existence of other unknown mechanisms that lead to an improvement of the cardiac performance[6] .

Aim

The study aims to demonstrate the effect of ivabradine on clinical, echocardiographic (diastolic function, left ventricular ejection fraction, ventricular volumes and echocardiogram-Color Doppler analysis with two-dimensional trans-thoracic strain and strain rate), electrocardiographic and serological (NT-proBNP) endpoints in DMD patients.

Materials and Methods

We included 30 patients (20 cases and 10 controls) from departments of Neuroscience AOU Policlinico Universitario G. Martino and the NEMO center of Messina.

Met the inclusion criteria (age 14-35 years; FE <50%), Ivabradine was administered at a dose of 5 mg/day in addition to optimized medical therapy. Were excluded patients with: Hypersensitivity to the active substance, Chronic or paroxysmal atrial fibrillation documented, Bradycardia (HR <60 bpm), AV Block, Sino-atrial block, Sick sinus syndrome, Poor Compliance.

At enrollment (STEP I, without ivabradine) and at follow-up (after 6 month of ivabradine) patients were undergo:

- ✓ Blood sampling for the determination of NT-proBNP,
- ✓ Cardiological examination,
- ✓ Electrocardiogram (ECG),
- ✓ Holter ECG,
- ✓ Echocardiogram-Color Doppler analysis with two-dimensional trans-thoracic strain and strain rate,
- ✓ Questionnaire (SF-12).

Results

Safety: Treatment was well tolerated in all patients, without side effect.

Efficacy: After a 6 month follow-up, we found in treated patients:

- Reduced heart rate ($p < 0.05$) (graph 1, 2, fig 2);
- A trend towards an improvement in ejection fraction (fig 3);
- A significant improvement in longitudinal fraction (S' wave) ($p < 0.05$) (fig 4);
- NT-proBNP were maintained in the normal range.
- An amelioration in quality of life in SF21 questionnaire analysis (fig 5).

The analysis of data about heart rate variability, left ventricular deformation (strain rate and strain rate) and LV remodeling are still ongoing.

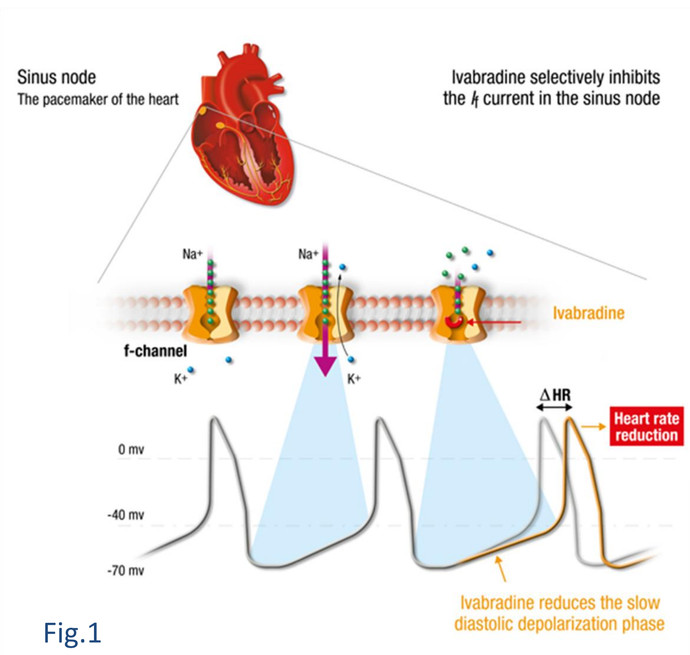
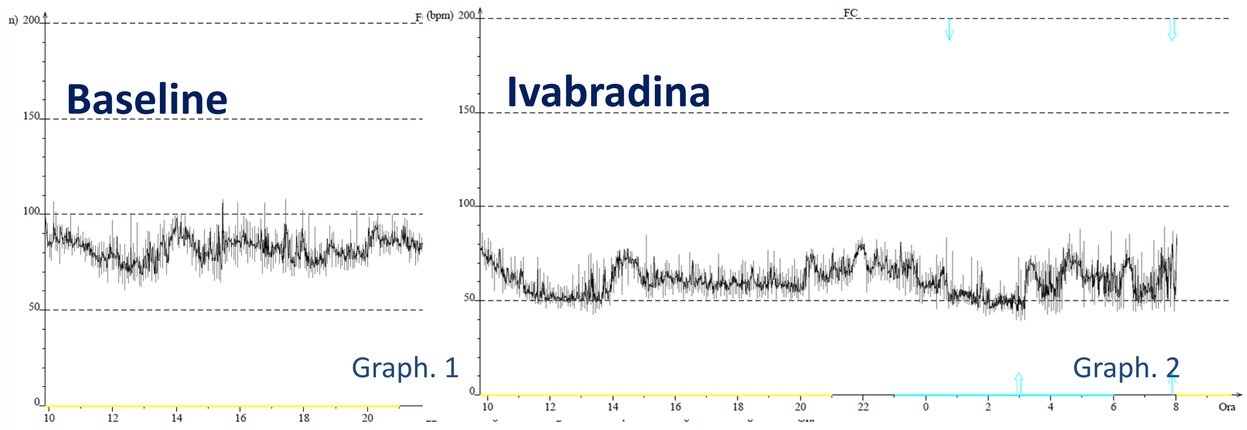


Fig.1



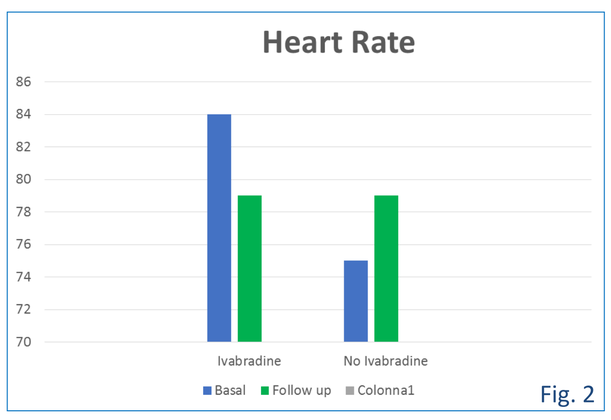


Fig. 2

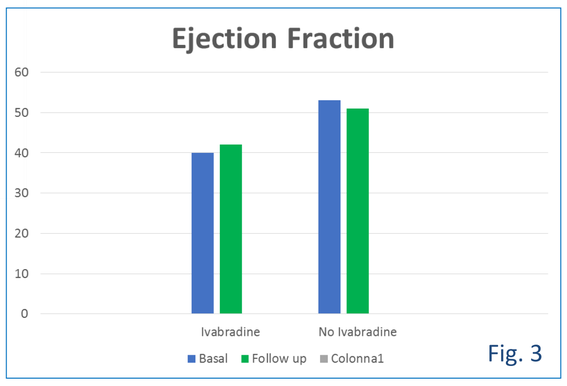


Fig. 3

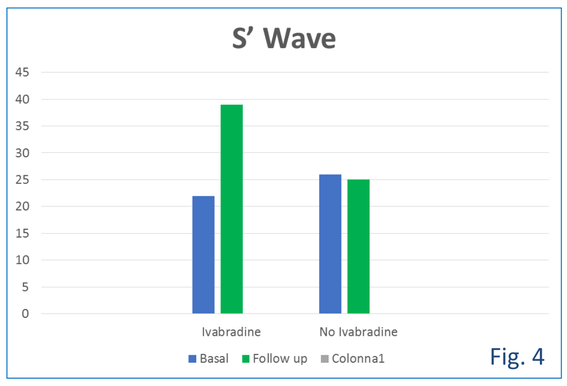


Fig. 4

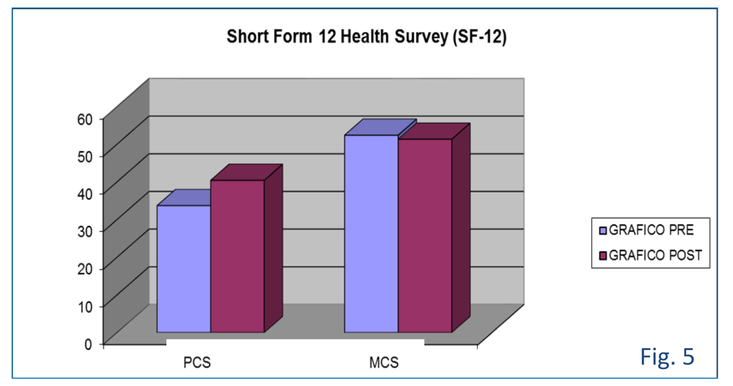


Fig. 5

Discussions and Conclusions

We confirmed the ivabradine effect in reducing heart rate in DMD patients, without altering other hemodynamic parameters such as blood pressure. We emphasized the positive impact on the quality of life with ivabradine treatment compared with the use of beta-blockers (as demonstrated by a SHIFT subtext) [7]. This seems to be due ivabradine ability to reduce myocardial oxygen consumption at peak stress, as previously proven at cardiopulmonary tests. Moreover, further analysis of data about heart rate variability, LV deformation and LV remodelling, can give us new interesting insights. Correlations with functional tests are ongoing. A robust methodology is needed to confirm these encouraging preliminary results.

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