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**CASE REPORT**
*Sports cardiology*

# Paradoxical improvement in exercise tolerance and peak VO2 consumption after treatment with ivabradine and beta-blockers in a patient with mild dilated cardiomyopathy and inappropriate sinus tachycardia—a case report

**Francesca Graziano [1,2], Matteo Pizzolato[1], Sergei Bondarev[1], Domenico Corrado [1], and Alessandro Zorzi [1]***

[1]Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padova, Via Giustiniani 2, 35128 Padova, Italy; and [2]Department of Sports Medicine, Semmelweis University, Gaál József út 9, 1122 Budapest, Hungary

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**Background** Left bundle branch block (LBBB) is a rare conduction disorder in athletes associated with ventricular dyssynchrony, which can lead to left ventricular systolic dysfunction and exercise intolerance. Inappropriate sinus tachycardia (IST) is characterized by an excessive heart rate (HR) that is not related to physiological needs, often resulting in reduced exercise capacity. Managing these conditions in athletes can be challenging, as standard treatments like beta-blockers and ivabradine, while effective in controlling HR, are described to be associated with a reduction in maximal exercise performance.

**Case summary** A 50-year-old amateur athlete presented with exercise intolerance, LBBB, and mild dilated cardiomyopathy due to ventricular dyssynchrony. Resting electrocardiogram and 24-h monitoring confirmed IST. Initial cardiopulmonary exercise testing (CPET) off-therapy showed rapid HR increase during exertion, an early plateau in oxygen pulse, and reduced peak oxygen consumption (VO2, 22.1 mL/kg/min, 76% of the predicted value). After 1 month of ivabradine 5 mg b.i.d., there was some improvement in these parameters. At the third follow-up, with combined therapy of ivabradine (5 mg b.i.d.) and metoprolol (50 mg b.i.d.), the HR response during exercise normalized, and CPET parameters significantly improved, with peak VO2 reaching 29.2 mL/kg/min (101% of the predicted value).

**Discussion** This case highlights a paradoxical improvement in exercise tolerance and peak VO2 with combined ivabradine and beta-blocker therapy in a patient with IST. The treatment optimized the HR response during exercise, suggesting that individualized strategies can enhance exercise performance in patients with IST and mild cardiomyopathy, despite the expected limitations of these medications.

**Keywords** Cardiopulmonary exercise testing • Dilated cardiomyopathy • Sports cardiology • Case report

**ESC curriculum** 8.1 Sports Cardiology • 5.5 Supraventricular tachycardia • 6.5 Cardiomyopathy

* Corresponding author. Tel: +39 049 821 2322, Email: alessandro.zorzi@unipd.it
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## Learning points

- The combination of ivabradine and beta-blockers may improve exercise tolerance in patients with inappropriate sinus tachycardia (IST) by optimizing the heart rate response to exertion and increasing stroke volume during exercise.
- This case highlights that, contrary to expectations, beta-blockers combined with ivabradine can enhance peak VO2 consumption in patients with IST, demonstrating the need for individualized treatment strategies.

# Introduction

Left bundle branch block (LBBB) is defined as a prolongation of the QRS complex >120 ms, with a predominantly negative component in V1 and an R wave pattern in leads DI and V6. This conduction disorder is quite rare (0.43% in men and 0.28% in women) in the general population[1]; its presence becomes even rarer among athletes[2] and among them is considered 'uncommon' and not related to training.[3] However, it can be associated with myocardial dysfunction, structural heart alterations, and/or coronary artery disease. Regardless of the underlying cause, LBBB is associated with left ventricular (LV) contraction dyssynchrony, playing an important role in ventricular remodelling, LV systolic dysfunction, progression to heart failure and increased mortality.[4–6] Cardiorespiratory fitness studies comparing subjects with isolated LBBB and non-LBBB on cardiopulmonary exercise testing (CPET) have demonstrated reduced exercise tolerance and peak oxygen consumption in subjects with the conduction disorder.[7,8]

# Summary figure

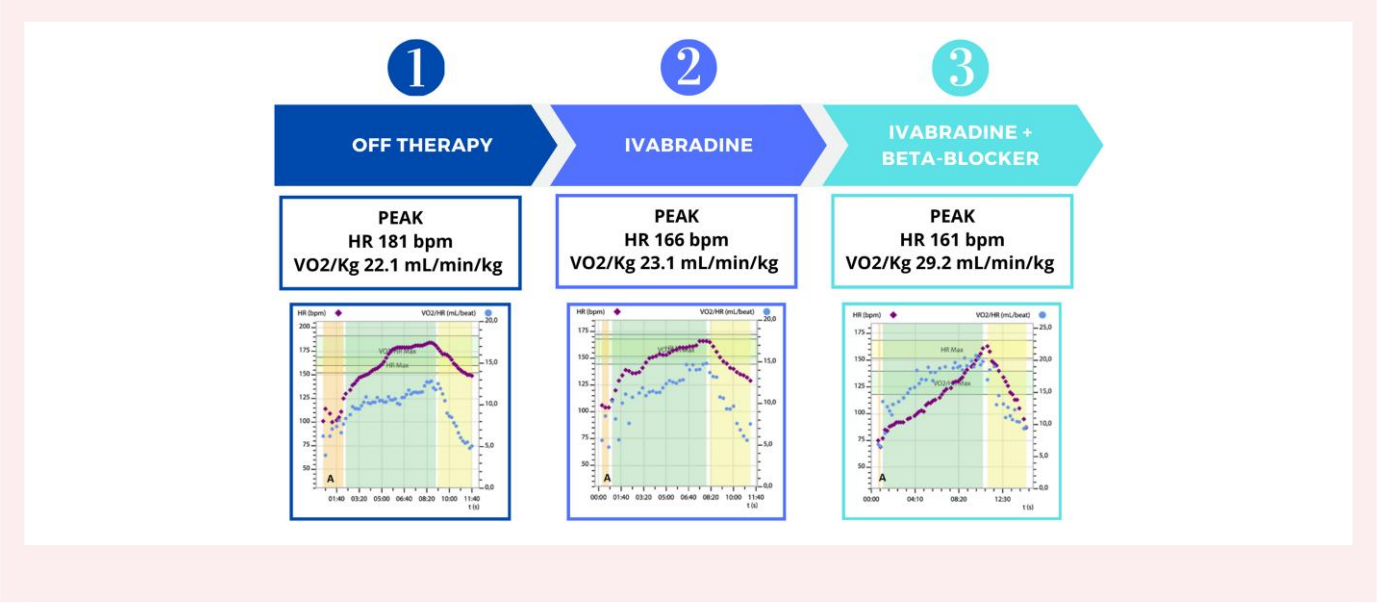
The introduction of ivabradine 5 mg b.i.d.[2] and metoprolol 50 mg b.i.d.[3] progressively reduced resting heart rate and mitigated the excessive chronotropic response to exertion, which led to an improvement in the oxygen pulse curve and, consequently, enhanced physical performance as evidenced by increased peak oxygen consumption.

Inappropriate sinus tachycardia (IST) is a syndrome characterized by sinus tachycardia unrelated to disease, physiological response, or drug therapy, and it can be associated with symptoms that may limit the quality of life. Diagnosis is made by exclusion. The underlying mechanism could be increased primary sinus node automatism or an abnormal autonomic response resulting in increased beta-adrenergic tone and subsequently increased sinus activity. Although IST does not necessarily correlate with underlying pathology, it is considered a maladaptive phenomenon.[9]

Pharmacological therapy is empirical and may require the use of beta-blockers, verapamil or I(f) channel blockers (ivabradine).[9] The latter was found to be superior for tolerability and capacity to improve exercise tolerance compared to beta-blockers.[10] However, ivabradine alone may perturb the feedback loop underlying baroreceptor control of autonomic balance, thereby increasing sympathetic activity to the heart. For this reason, the current European Society of Cardiology (ESC) guidelines on supraventricular arrhythmias suggest that the combination of ivabradine and a beta-blocker (at lower, better-tolerated doses) could be the preferred therapeutic option.[11] However, no data are available on the effect of this combination therapy on the heart rate (HR) response profile to exercise and cardiorespiratory fitness. All relevant data underlying this article are available in the text.

# Case presentation

A 50-year-old male amateur soccer player (training twice a week for 1.5 h and playing a match once a week), was referred to our sports cardiology clinic due to reduced exercise tolerance. His family history was negative for heart disease and sudden death. He reported consuming only one, at most two, cups of espresso per day and not using any other stimulants, denied taking any performance-enhancing drugs or dietary supplements, and the clinical examination did not reveal any signs suggestive of concealed use of such substances. Blood tests showed normal values for the complete blood count, including haematocrit, γ-glutamyl transpeptidase, and cholesterol levels, further supporting the absence of substance abuse.[12] Additionally, thyroid function tests, including TSH, fT3, and fT4 levels, were within normal ranges.



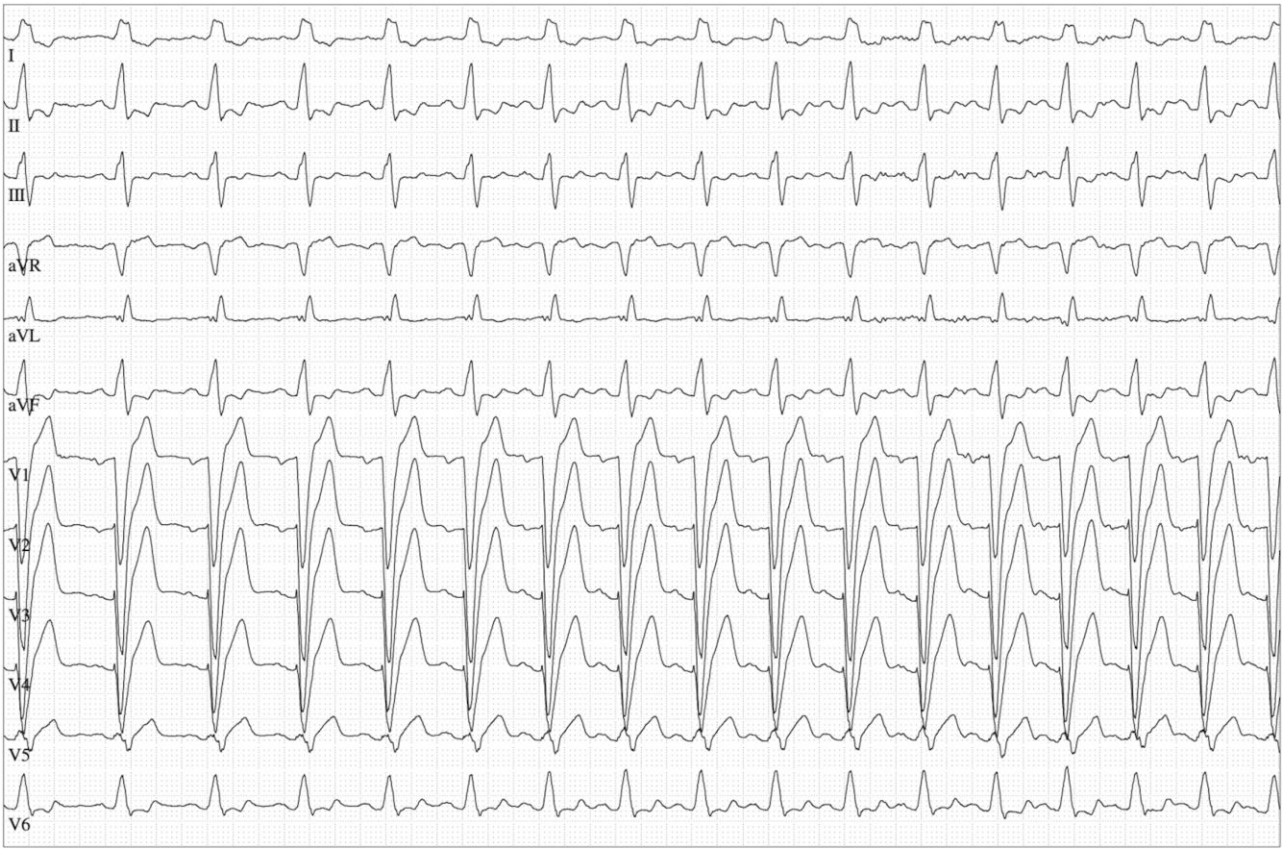



**Figure 1** Resting electrocardiogram in the supine position. Inappropriate sinus tachycardia (heart rate 105 b.p.m.) and left bundle brunch block.

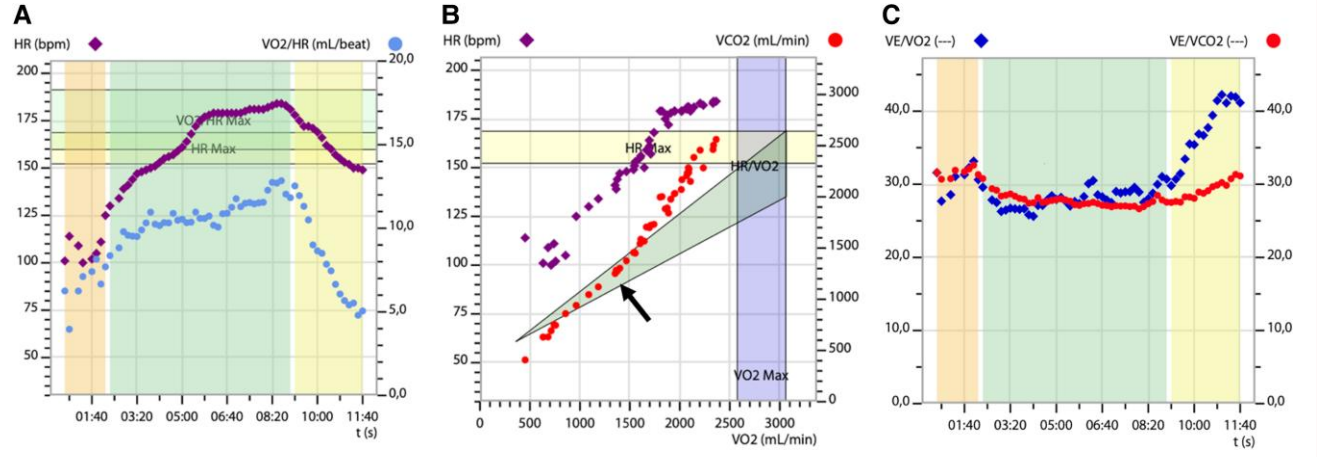



**Figure 2** Cardiopulmonary exercise testing graphs obtained during the first test (off-therapy) with a ramp protocol of 20 W/min. Heart rate (HR) and oxygen pulse (VO2/HR) over time (*A*); heart rate (HR) and carbon dioxide production (VCO2) over oxygen consumption (VO2) (*B*); ventilation/oxygen consumption (VE/VO2) and ventilation/carbon dioxide production (VE/VCO2) over time (*C*). The black arrow indicates the first ventilator threshold.

**Table 1** **Selected cardiopulmonary testing parameters obtained during the first (off-therapy), second (ivabradine 5 mg b.i.d.), and third (ivabradine 5 mg b.i.d. + metoprolol 50 mg b.i.d.) test**

| | Resting | | | Vent. Thr. 1 | | | Peak | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Off therapy** | **Ivabradine** | **Ivabradine + BB** | **Off therapy** | **Ivabradine** | **Ivabradine + BB** | **Off therapy** | **Ivabradine** | **Ivabradine + BB** |
| Effort | | | | | | | | | |
| *T* (s) | 0 | 0 | 0 | 03:40 | 04:15 | 05:30 | 07:20 | 08:42 | 10:37 |
| Power (W) | 0 | 0 | 0 | 80 | 100 | 120 | 160 | 180 | 220 |
| Metabolic | | | | | | | | | |
| $VO_2$ (mL/min) | 784 | 656 | 488 | 1555 | 1704 | 1843 | 2344 | 2471 | 3100 |
| VO2/kg (mL/min/kg) | 7.4 | 6.2 | 4.6 | 14.7 | 16.1 | 17.4 | 22.1 | 23.1 | 29.2 |
| RQ | 0.98 | 0.89 | 0.82 | 0.93 | 0.97 | 0.96 | 1.10 | 1.09 | 1.23 |
| Ventilatory | | | | | | | | | |
| $VE/VCO_2$ | | | | 26.4 | 27.3 | 24.5 | | | |
| VE (L/min) | 24 | 19.6 | 14.6 | 40.9 | 49.4 | 55.8 | 67 | 77 | 86 |
| Cardiovascular | | | | | | | | | |
| HR (b.p.m.) | 105 | 103 | 72 | 153 | 150 | 100 | 181 | 166 | 161 |
| $VO_2$/WR slope (mL/min/W) | | | | | | | 8.0 | 9.9 | 10.9 |
| Oxygen pulse, $VO_2$/HR (mL/beat) | 7.2 | 6.3 | 6.8 | 10.2 | 11.4 | 18.4 | 13.1 | 14.8 | 19.3 |
| Gas exchange | | | | | | | | | |
| $PETCO_2$ (mmHg) | 37 | 35 | 35 | 41 | 40 | 42 | 42 | 40 | 36 |

All three tests were performed on the same bike and with the same protocol (ramp with 20 W/min increments).
BB, beta-blockers; $CO_2$, carbon dioxide; HR, heart rate; $O_2$, oxygen; PET, end-tidal pressure; RQ, respiratory quotient; VE, ventilation; $VO_2$, oxygen consumption; WR, work rate.

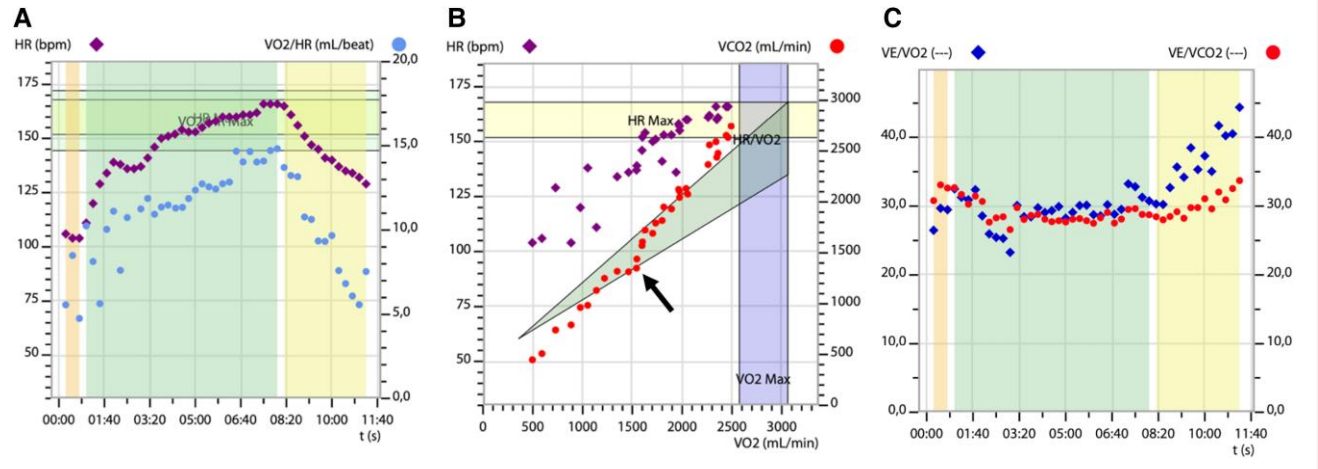



**Figure 3** Cardiopulmonary exercise testing graphs obtained during the second test (ivabradin 5 mg b.i.d.) with a ramp protocol of 20 W/min. Heart rate (HR) and oxygen pulse (VO2/HR) over time (*A*); heart rate (HR) and carbon dioxide production (VCO2) over oxygen consumption (VO2) (*B*); ventilation/oxygen consumption (VE/VO2) and ventilation/carbon dioxide production (VE/VCO2) over time (*C*). The black arrow indicates the first ventilator threshold.

Ten years prior to our first evaluation he was incidentally found to have a LBBB. The conduction disturbance was initially intermittent (depending on HR) and the echocardiogram was normal but later became persistent and associated to mild reduction in the LV ejection fraction (EF = 48%). Coronary computed tomography angiography showed normal coronary arteries and cardiac magnetic resonance revealed mild LV dilation/dysfunction secondary with evident mechanical dyssynchrony on cine and phase contrast images and no tissue characterization alterations. Genetic testing for mutations associated with cardiomyopathies was negative. This clinical scenario appeared compatible with early-stage dilated cardiomyopathy related to conduction disorder (so-called 'dyssynchrony cardiomyopathy').[13]

As the patient reported a reduction in exercise tolerance that did not seem proportionate with the mild heart disease, we performed an initial CPET on a cycle ergometer. At the time of the evaluation, he was not on pharmacological therapy due to reported intolerance.

Pre-exam electrocardiogram in the supine position (*Figure 1*) showed inappropriate sinus tachycardia (resting HR 105 b.p.m.). The exercise test revealed a very early achievement of a high HR: the athlete reached 153 b.p.m. at the first respiratory threshold, equivalent to 90% of the predicted maximum HR per age, with a maximal HR 181 b.p.m., equal to 108% of the theoretical maximum for age. This was followed by a near-plateau in both HR and oxygen pulse (a surrogate for stroke volume), indicating a limited capacity to further increase cardiac output during exertion (*Figure 2A*). Peak oxygen consumption was below expected (VO2max 22.1 mL/min/kg, equal to 76% of the predicted value). Functional limitation prevented visualization of the second ventilatory threshold (*Figure 2C* and *Table 1*). A subsequent 24-h Holter confirmed inappropriate sinus tachycardia with a stable average daytime HR above 100 b.p.m.

Ivabradine therapy was prescribed, and CPET was repeated: we observed a slight improvement in peak oxygen consumption (VO2max 23.1 mL/min/kg, equal to 80% of the predicted value) and a reduction in max HR (166 b.p.m., 99% of the predicted maximum). Again, it was not possible to visualize the second ventilatory threshold (*Figure 3* and *Table 1*).

As the HR profile concerning exertion was not yet satisfactory, metoprolol 50 mg b.i.d. was also prescribed. At the third follow-up (ivabradine + beta-blocker), 1 month after the previous one, there was a marked improvement in the maximum workload achieved (220 W vs. 160 W at the first check), oxygen consumption (29.2 mL/min/kg, 101% of the predicted value), a continuously increasing oxygen pulse curve with a further reduction in peak HR (max HR 161 b.p.m.) (*Figure 4A and B*). Additionally, the improved overall exercise capacity translated into greater exploitation of anaerobic lactate metabolism (indicated by visualization of the second ventilatory threshold) (*Figure 4C*). There were no changes in indirect parameters of diastolic function (VE/VCO2 slope, PetCO2) or saturation between the various tests, while the greater exploitation of stroke volume from the first to the last test was accompanied by increased maximum ventilation (*Table 1*). Blood pressure after beta-blocker therapy did not decrease, and its response to exercise was adequate. Finally, a control 24-h Holter on therapy was satisfactory (24-h average HR: daytime 65 b.p.m., night time 55 b.p.m.).

## Discussion

We presented the case of an amateur athlete diagnosed with mild dilated cardiomyopathy related to a conduction disorder (LBBB) with inappropriate sinus tachycardia.

Although a definite cause–effect relationship cannot be established with certainty, we hypothesized that sinus tachycardia may have represented an inappropriate response to reduced oxygen delivery, driven by reduced stroke volume secondary to LV dyssynchrony. As demonstrated by off-therapy CPET, this phenomenon was more responsible for poor exercise tolerance and reduced oxygen consumption than the mild reduction in LV EF. Indeed, the elevated HR in IST can impair diastolic filling time, leading to reduced stroke volume and an inefficient increase in cardiac output. The mismatch between oxygen supply and demand results in reduced exercise capacity, with symptoms such as fatigue and shortness of breath. Furthermore, the excessive HR elevates myocardial oxygen consumption, worsening the imbalance and contributing to exercise intolerance.[9]

The use of drugs that reduced resting HR and mitigated excessive chronotropic response to exertion allowed optimization of the HR/work curve and a physiological increase in stroke volume during exercise (evidenced by improvement in the oxygen pulse curve) and,

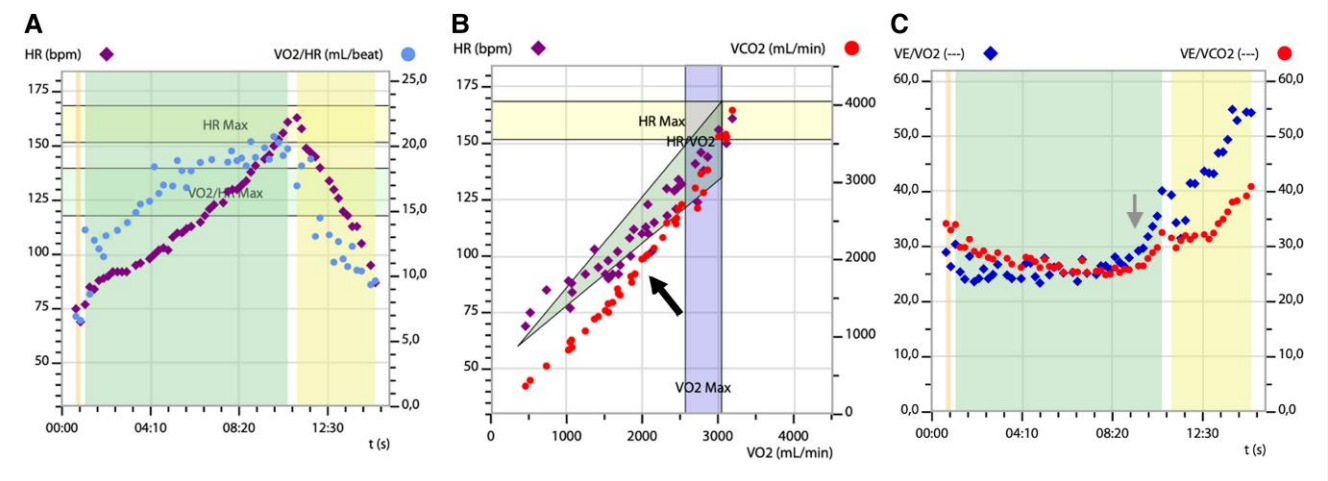



**Figure 4** Cardiopulmonary exercise testing graphs obtained during the third test (ivabradin 5 mg b.i.d. plus metoprolol 50 mg b.i.d.) with a ramp protocol of 20 W/min. Heart rate (HR) and oxygen pulse (VO2/HR) over time (*A*); heart rate (HR) and carbon dioxide production (VCO2) over oxygen consumption (VO2) (*B*); ventilation/oxygen consumption (VE/VO2) and ventilation/carbon dioxide production (VE/VCO2) over time (*C*). The black arrow indicates the first ventilator threshold, the grey arrow the second ventilator threshold.

consequently, improved physical performance, evidenced by increased peak oxygen consumption, maximum ventilation, and exercise tolerance. This effect was more evident when beta-blocker therapy was added. Consistent with the literature, we hypothesized that the use of ivabradine alone was insufficient because it may induce a further increase in beta-adrenergic response (attempting to maintain tachycardia), which can be inhibited with the use of beta-blockers.[11]

In conclusion, we described a case of inappropriate sinus tachycardia where the combined administration of ivabradine and metoprolol resulted in a significant improvement in peak oxygen consumption. This effect is paradoxical since beta-blocker therapy generally reduces or, at most, maintains peak oxygen consumption.[14–16]

## Patient perspective

At first, I was reluctant to start drug therapy because in the past I had tried the combination of ramipril/bisoprolol and did not tolerate it well. However, with the ivabradine/metoprolol combination, I immediately felt better. I have not experienced any drops in blood pressure, my pulse is steadier, and above all, I can exercise for much longer and with less fatigue.

## Lead author biography

Dr Francesca Graziano graduated from the University of Siena, Italy. She completed her Cardiology residency at the University of Padova, Italy. She is currently a Research Fellow at the University of Padova and a PhD student at Semmelweis University, Hungary. Her research interests include cardiomyopathy and sports cardiology, with a special focus on cardiopulmonary exercise testing and cardiac magnetic resonance.

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## Consent

The authors confirm that written consent for submission and publication of this case report has been obtained from the patient in line with the Committee on Publication Ethics guidance.

**Conflict of interest:** None declared.

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## Data availability

Data underlying this article will be shared on reasonable request to the corresponding author.

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