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CASE REPORT

ADVANCED

CLINICAL CASE: SPORTS CARDIOLOGY

A Cyclist on a Tricyclic

Exercise Intolerance Due to Chronotropic Incompetence

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ABSTRACT

Depression in athletes is prevalent, and antidepressant treatment may have a cardiovascular impact. We present a case, documented by serial exercise testing, of exertional intolerance due to chronotropic incompetence associated with tricyclic antidepressant use. This case underscores the importance of understanding the mechanism of action and side effects of antidepressants. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:1335–1340)

A 46-year-old male competitive road cyclist with a history of depression presented with decreased exercise tolerance. Over the previous year he had lost the ability to sustain a high level of effort during rides, especially hill climbs. He noted a reduction in his heart rate (HR) on a wearable device from 170 beats/min to 150 beats/min during maximal perceived exertion. He noticed that his HR at all levels of submaximal exertion was lower. He did not note lower resting HR, felt well with routine activities, and did not describe any coincidental illnesses. His training volume and intensity had been consistent over several years. He did not describe chest pain, dyspnea, palpitations, lightheadedness, or syncope.

LEARNING OBJECTIVES

- To generate a differential diagnosis for chronotropic incompetence, including that specific to an otherwise healthy athlete.
- To understand the importance of using the known mechanisms of action of non-cardiovascular drugs to identify uncommon but impactful cardiovascular side effects.
- To appreciate the high value of longitudinal repeated-measures testing—here, cardiopulmonary exercise testing—in identifying the impact of interventions.

Upon further questioning, he reported that his long-standing depression had been difficult to manage. One year previously, he had started 3 new medications: bupropion 200 mg twice daily, desipramine 150 mg daily, and clonazepam 0.5 mg as needed. The initiation of this regimen improved his depression but coincided with the onset of his exertional symptoms. He had normal vital signs and physical examination results, including a cardiovascular examination that revealed a regular rate and rhythm and no murmurs, rubs, or gallops.

MEDICAL HISTORY

He did not disclose any other medical history, and there was no family history of cardiovascular illness. He did not describe smoking or use of alcohol, drugs, or performance-enhancing agents.

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ABBREVIATIONS AND ACRONYMS

CNS = central nervous system

CPET = cardiopulmonary exercise test

HR = heart rate

HRR = heart rate reserve

RER = respiratory exchange ratio

TCA = tricyclic antidepressant

VE = minute ventilation

VO_2 = oxygen consumption

DIFFERENTIAL DIAGNOSIS

We considered and evaluated for multiple potential causes of this patient's exertional intolerance, including arrhythmia, structural heart disease, and ischemic heart disease. Given the exertional nature of his symptoms, we focused on obtaining a cardiopulmonary exercise test (CPET), which as detailed below confirmed the presence, as suggested by the patient's wearable device, of chronotropic incompetence. We then considered and evaluated for multiple potential diagnoses for chronotropic incompetence (Table 1). Because symptom onset corresponded with the initiation of new medications, we reviewed their mechanisms and potential side effects. The patient was not consistently using clonazepam, and its use did not correspond with his symptoms. Chronotropic incompetence is not a reported side effect of desipramine, a tricyclic antidepressant (TCA), or of bupropion, a norepinephrine-dopamine reuptake inhibitor. However, down-regulation of central nervous system (CNS) β1 receptors has been reported as a potential mechanism of therapeutic action for TCAs.[1,2] We hypothesized that if similar down-regulation of β1 receptors occurs in the heart, the patient's desipramine could be the cause of his chronotropic incompetence.

TABLE 1 Differential Diagnosis

Causes of Chronotropic Incompetence	Reason Excluded
Sinus node dysfunction	Rare in younger patients
Myocardial ischemia	No ischemia on CPET
Heart failure	No evidence in history, cardiac examination
Hypothyroidism	Normal thyroid test results
Medications	Cannot exclude

CPET = cardiopulmonary exercise test.

INVESTIGATIONS

Thyroid hormone level, basic metabolic panel results, and complete blood count were within normal limits. The patient's electrocardiogram showed normal sinus rhythm at 74 beats/min, left axis deviation, and normal intervals (Figure 1). A transthoracic echocardiogram was normal. The patient underwent a maximal-effort, graded CPET on an upright cycle ergometer (Figure 2). He achieved a peak work of 346 watts and peak oxygen consumption (VO_2) of 47 mL/kg/min (134% predicted) at an adequate effort respiratory exchange ratio (RER) of 1.2. His HR increased linearly with graded exercise but reached only 145 beats/min, or 83% of age-predicted maximal HR (Figure 3A), with an abnormally high heart rate reserve (HRR) of 29 beats/min and low chronotropic index of 0.65 (normal range 0.8-1.3). The chronotropic index was calculated using the following formula: ([achieved maximal HR − resting HR]/[age-predicted maximal HR − resting HR]).[3] Other CPET parameters were within normal limits (Table 2, Figure 2).

FIGURE 1 Baseline 12-Lead Electrocardiogram

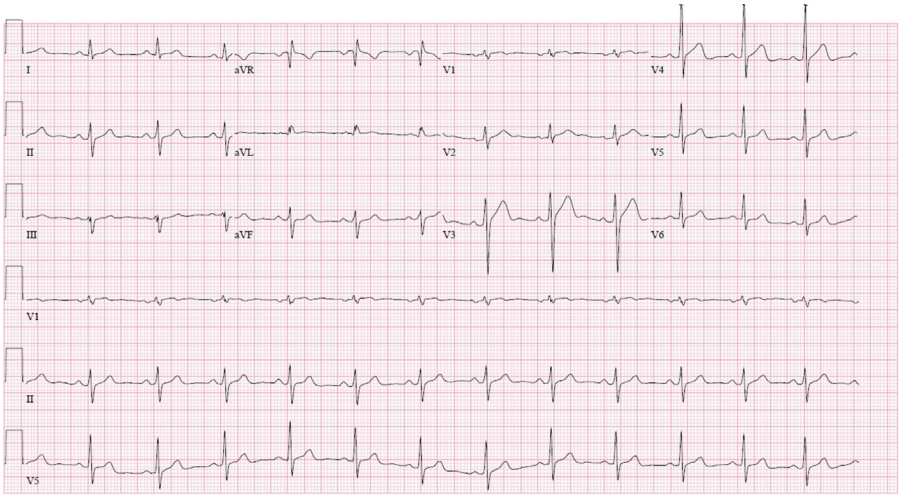
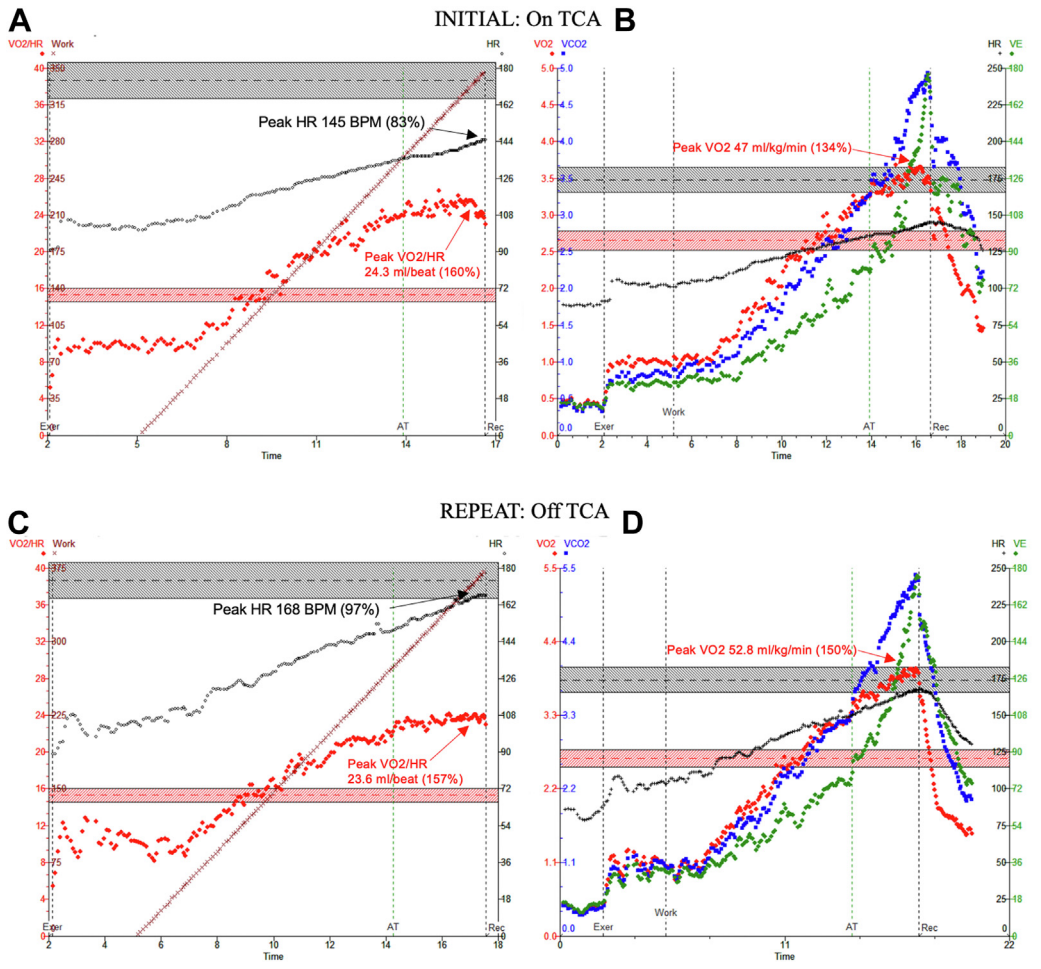


FIGURE 2 **Serial Cardiopulmonary Exercise Tests**



(A, C) HR **(black dots)**, O_2 pulse **(red dots)**, and work wattage **(dark red crosses)** during graded exercise. **Black and red hashed bars** depict 95% to 105% predicted peak HR and O_2 pulse, respectively. **Green dotted line** is the estimated VT or AT. **(B, D)** VO_2 **(red)**, VCO_2 **(blue)**, HR **(black)**, and VE **(green)** during graded exercise. **Black and red hashed bars** depict 95% to 105% predicted peak HR and VO_2, respectively. AT = anerobic threshold; HR = heart rate; TCA = tricyclic antidepressant; VCO_2 = carbon dioxide production; VE = minute ventilation; VO_2 = oxygen consumption; VT = ventilatory threshold.

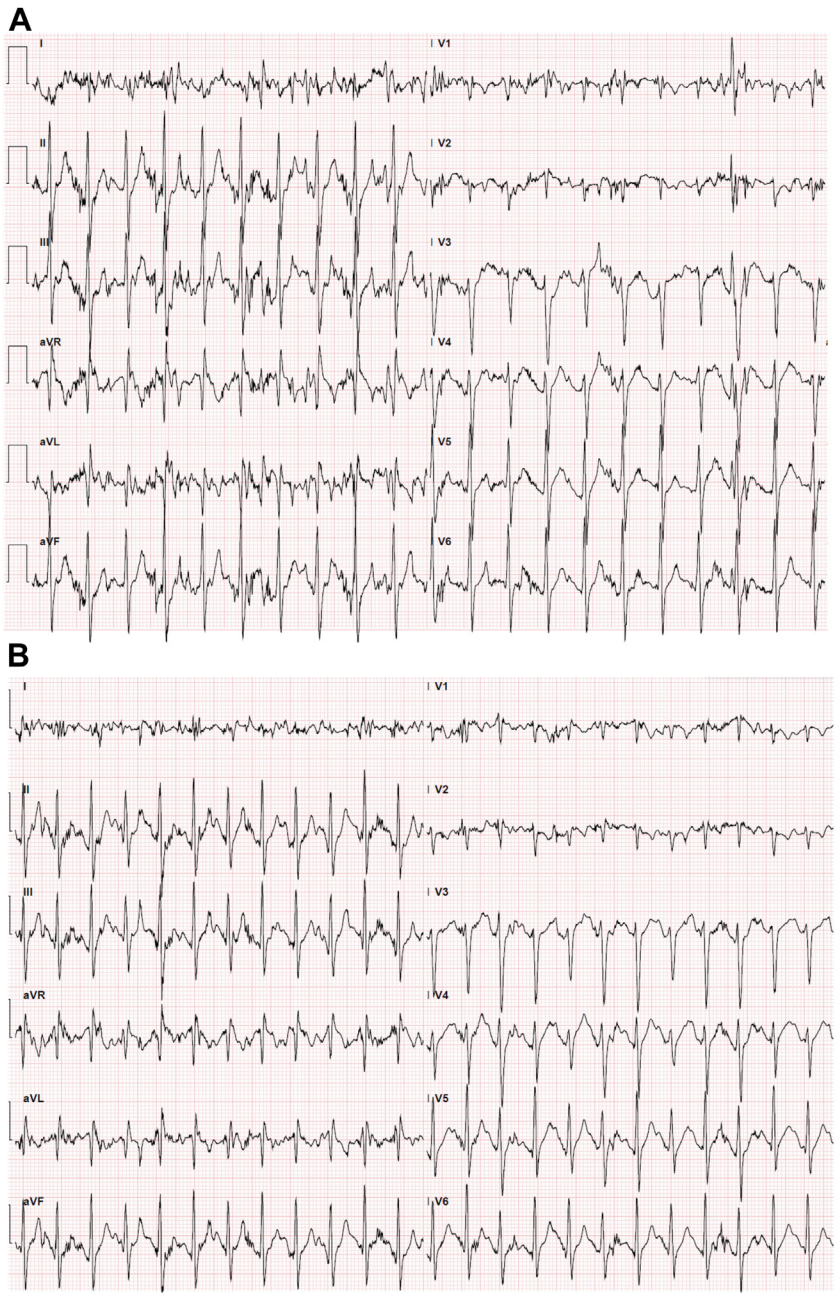
MANAGEMENT

After shared decision making that included the patient, cardiology team, and psychiatry team, desipramine was tapered off to ascertain whether it was the cause of his exertional intolerance. Over this period, the patient maintained his usual training regimen and did not change his other medications. One week after cessation of desipramine, he underwent a repeated CPET using an identical protocol to his first test (Figure 2). He exercised to a higher peak work (371 w) and peak VO_2 (52.8 mL/kg/min, 150% predicted) with similar RER (1.2). Most importantly, his peak HR increased to the normal range (168 beats/min, 97% predicted) (Figure 3B) with a significantly reduced HRR of 6 beats/min and improvement of chronotropic index to 0.94. His HR on his resting 12-lead electrocardiogram was similar to baseline (70 beats/min).

DISCUSSION

The prevalence of depression in athletes has been understudied but appears to be the same as, or possibly higher than, in nonathletes.[4] TCAs at a high dose, as in our patient, have been used for depression since 1957. However, given their greater risk of

FIGURE 3 Cardiopulmonary Exercise Test Electrocardiogram Tracings



(A) Peak HR on TCA, 145 beats/min. **(B)** Peak HR off TCA, 168 beats/min. HR = heart rate; TCA = tricyclic antidepressant.

toxicity, TCAs are now second line to newer agents. The antidepressant mechanism of TCAs is thought to be augmentation of serotonin and/or norepinephrine transmission by inhibiting the transporters responsible for the reuptake of these monoamines. However, TCAs also act on many other receptors, including those for catecholamines.

Although TCA toxicity has been reported to lead to complete heart block, to our knowledge this is the first reported case of chronotropic incompetence

associated with therapeutic TCA use. This side effect is mechanistically plausible. In animal models, TCA both decreases the sensitivity and reduces the number of CNS β1 receptors.[5] Because TCAs block the reuptake of norepinephrine, the resultant elevation in norepinephrine levels at the synapse mediates this desensitization and down-regulation of β1 receptors.[6] Reduction in β receptor sensitivity and density is also seen with long-term TCA administration in humans and correlates with time to a clinical response to depression treatment.[7] One prior study suggests similar impairment in cardiac β1 receptor activity, as is seen in the CNS, with TCA use. Specifically, when the effect of isoproterenol on HR response in healthy male individuals was examined before, during, and after treatment with desipramine, the isoproterenol dose required to increase the resting HR by 25 beats/min was significantly higher after 2 weeks of 75 mg desipramine daily.[8] This study supports our hypothesis that desipramine was responsible for the patient's chronotropic incompetence, as evidenced by the restoration of normal peak HR upon drug discontinuation.

Athletes are especially sensitive to blunting of peak HR because, whereas at low intensities both HR and stroke volume increase together to increase cardiac output (CO), further augmentation of cardiac output at high-intensity efforts is primarily due to increases in HR. An abnormal limitation in peak HR reduces peak achievable CO and therefore also peak exercise capacity. In this case, the use of gas exchange was particularly appropriate because it clearly demonstrated this physiology with improvement in peak VO_2 that mirrored those in peak HR and because it allowed for exclusion of poor volitional effort from the differential for the low peak HR via use of the RER.

FOLLOW-UP

After TCA discontinuation, the patient noted improved exercise tolerance and normalization of exercise HRs into his usual range. After discussion with his psychiatrist, he began to take a different antidepressant that provided adequate control of his depression. He has not had recurrence of his exertional symptoms.

TABLE 2 CPET Parameters

	Initial (On TCA)	Repeat (Off TCA)
Exercise time, min	14:33	15:32
Peak work, W (% predicted)	346 (173)	371 (186)
Peak RER, dimensionless	1.2	1.2
Peak VO_2, L/min (% predicted)	3.53 (134)	3.97 (150)
Peak VO_2, mL/kg/min (% predicted)	47 (134)	52.8 (150)
Heart rate, before exercise, beats/min	90	79
Heart rate, peak, beats/min (% predicted)	145 (83)	168 (97)
Heart rate reserve, beats/min	29	6
Chronotropic index, dimensionless	0.65	0.94
Peak O_2 pulse, mL/beat (% predicted)	24.3 (160)	23.6 (157)
VE/VCO_2 at ventilatory threshold, dimensionless	23.3	20.6
VE/VCO_2 total slope, dimensionless	30.1	27

CPET = cardiopulmonary exercise test; RER = respiratory exchange ratio; TCA = tricyclic antidepressant; VCO_2 = carbon dioxide production; VE = minute ventilation; VO_2 = oxygen consumption.

CONCLUSIONS

We describe a case in which TCA use was associated with chronotropic incompetence. Based on available data, this is likely due to reduction in the sensitivity or density of cardiac β1 receptors, which is consistent with the known CNS effect of TCAs. We speculate that this side effect has not been previously reported because high-dose TCA use is currently uncommon, and our patient's presentation was subtle, with symptoms occurring only at moderate- to high-intensity exercise. This highlights the importance of comprehensive evaluation of the athlete with cardiovascular symptoms, including, in this case, a longitudinal repeated-measures evaluation using precisely controlled exercise testing to evaluate a specific hypothesis. Chronotropic incompetence should be considered a potential side effect of TCAs in those with a suggestive history.

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KEY WORDS exercise, lifestyle, treatment