

# A unique cardiovascular presentation of pheochromocytoma

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## Abstract

We describe a unique presentation of a pheochromocytoma in a normotensive teenager, who presented with symptoms of headache, neck pain, and palpitations. Holter and event monitor tracings revealed intermittent junctional rhythm causing electromechanical dyssynchrony between atrial and ventricular contraction resulting in reported symptoms. Exercise stress testing helped correlate symptomatic junctional rhythm events to episodic hypertension which led to the eventual diagnosis of pheochromocytoma. The exercise test provided insight into the physiologic coupling that the sympathetic and parasympathetic autonomic nervous systems have on the cardiovascular system during exercise and exaggerated hypertension. The patient was found to have MEN2A and partial adrenalectomy resulted in complete resolution of symptoms and arrhythmia. This unusual presentation illustrates the benefit of a comprehensive clinical evaluation, which led to the eventual diagnosis.

## Keywords

Pediatrics, electrophysiology, arrhythmia

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## Introduction

Pheochromocytomas are catecholamine-secreting tumors that along with a multitude of systemic symptoms can cause heterogeneous cardiovascular manifestations including hypertension palpitations, tachycardia, chest pain, orthostatic hypotension, and electrocardiographic (ECG) changes.<sup>1</sup> Tachyarrhythmias, including junctional tachycardia, have also been described as a presenting sign of pheochromocytoma or paraganglioma in children.<sup>2–5</sup> However, junctional rhythm without tachycardia, as the predominant rhythm, has rarely if ever been reported in children. We describe a unique presentation of a pheochromocytoma in a teenager who presented with symptomatic intermittent junctional rhythm without tachycardia. Upon further workup, a pheochromocytoma was diagnosed after hypertension was elicited on an exercise stress test (EST).

## Case report

A 16-year-old, 63-kg Caucasian female with a history of asthma and allergic rhinitis presented in May 2019 to a pediatric cardiology clinic with a 5-month history of daily palpitations. The palpitations were characterized as hard, pounding heart beats that were associated with neck and jaw

discomfort, headaches, shortness of breath, and dizziness. Symptoms would occur at rest, last for several minutes, and then self-resolve. They were not rapid and did not occur with exercise. On evaluation, her heart rate was 80 bpm, BP 121/62, and the remainder of her physical exam was normal. Her baseline electrocardiogram (ECG) demonstrated sinus rhythm at 60 bpm and an echocardiogram revealed a structurally and functionally normal heart. A 48-h Holter monitor was placed with symptomatic events capturing sinus rhythm and possible junctional rhythm.

Six months later, the patient returned and reported a change in the character of the palpitations, which now occurred with exercise and on occasion would wake her from sleep. A looping event monitor was issued and captured numerous symptom episodes (heart pounding, jaw pain, and headache), predominantly associated with junctional rhythm

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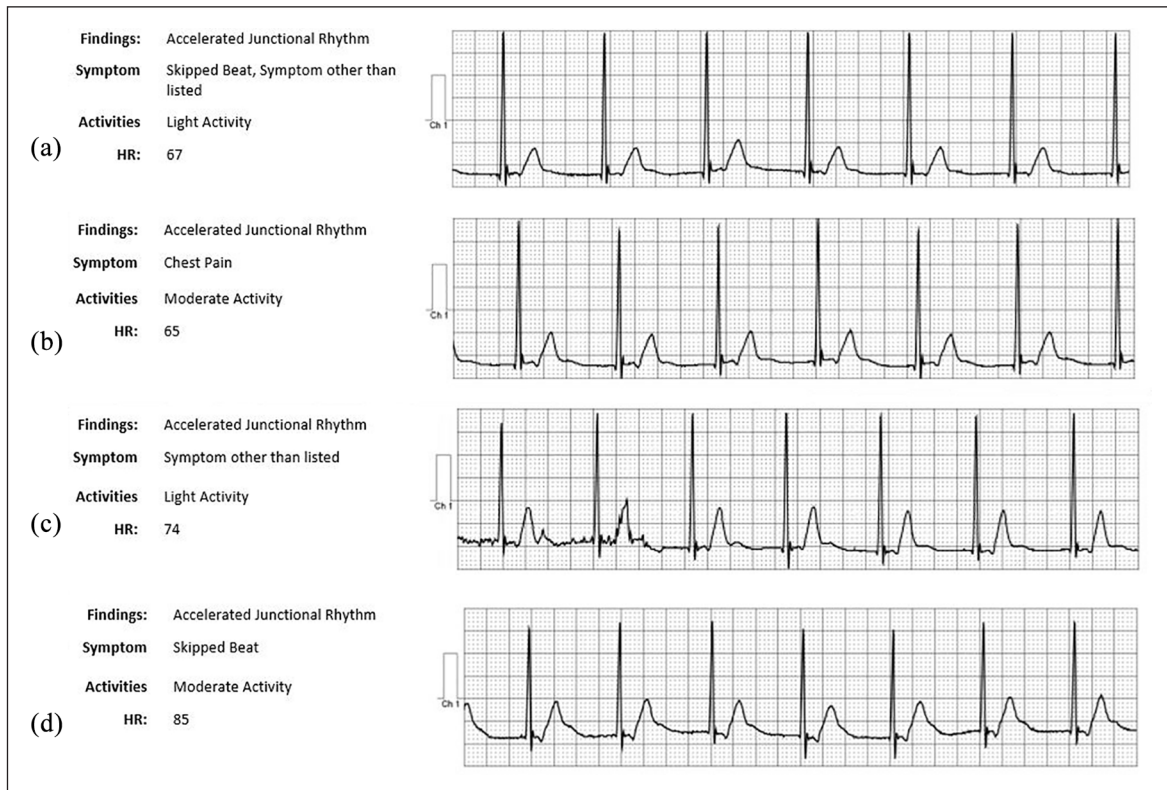
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**Figure 1.** Multiple captured symptomatic events on looping event monitor. (a–d) Symptomatic events captured by the event monitor revealing junctional rhythm between 65 and 85 bpm.

with rates between 50 and 80 bpm. Asymptomatic events captured sinus tachycardia with rates between 167 and 179 bpm. At this point, the symptoms were thought to be secondary to an exaggerated right atrial and central venous pressure caused by atrioventricular dyssynchrony associated with junctional rhythm (Figure 1). The patient was trialed on atenolol 12.5 mg once daily to determine whether her symptoms and rhythm could be explained by an ectopic junctional focus. This was discontinued 2 weeks later due to side effects of irritability, fatigue, and worsening headaches.

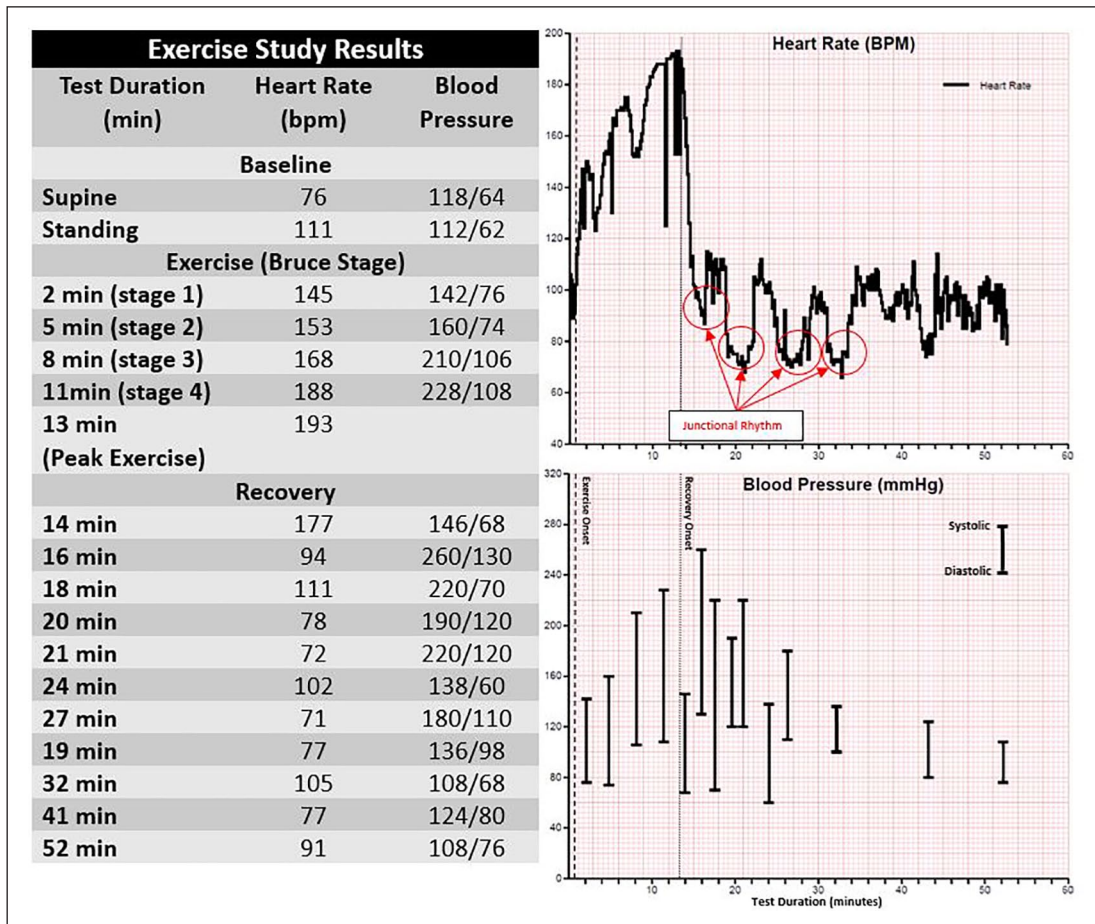
Her symptoms continued to escalate, with increased frequency of symptomatic events now occurring during both activity and rest, resulting in her inability to participate in organized sports. She was referred to Pediatric Electrophysiology Clinic in February 2020 for evaluation, which included an EST.

The EST was performed using the standard Bruce protocol on a treadmill. Institutional protocol is to obtain supine and standing ECGs with manual non-oscillometric blood pressures. During the test, continuous ECG is recorded along with a manual blood pressure measurement during each stage, including recovery. The patient's baseline rhythm and BP were normal at the start of the stress test. As exercise intensity progressed, there was an appropriate heart rate response, demonstrated by sinus tachycardia at a peak rate of 193 bpm (94% predicted) and significant systolic and

diastolic hypertension with a peak of 228/106, though the patient remained asymptomatic during the exercise phase. However, during the recovery phase, she reported symptoms of headache, dizziness, neck pain, and chest pain, which were associated with hypertension and junctional rhythm (Figure 2). Episodic hypertension and junctional rhythm continued throughout recovery. The study was terminated after monitoring the patient for 30 min into recovery.

Given her abnormal blood pressure response on her EST during both exercise and recovery, with a normal physical exam (including femoral pulses) and previous normal echocardiogram ruling out coarctation of the aorta, additional causes of hypertension were considered, including a pheochromocytoma. Both blood and urine metanephrines were ordered and found to be abnormal: urine total, blood metanephrines, and blood normetanephrines were elevated at 9841 mcg/24 h (lab reference range: normal 33–185 mcg/24 h), serum 13 nmol/L (lab reference range <0.5 nmol/L), and 5.8 nmol/L (lab reference range <0.9 nmol/L), respectively. Given the abnormal results, a computerized tomography scan was ordered and confirmed the presence of a 5.2 × 6.0 × 5.7 cm left adrenal mass.

The patient was subsequently referred to endocrinology with eventual tumor resection after treatment with phenoxybenzamine to 50 mg QID and metyrosine to 500 mg for 1 month prior to surgery. Genetic testing revealed the



**Figure 2.** Exercise study results in table format documenting the heart rate and blood pressure during the test next to the identical measurements graphed. Red circles indicating junction rhythm are the times during recovery when the heart rhythm was junctional.

patient was heterozygous for a pathogenic variant in *RET* (c.1826G>A (p. Cys609Tyr)) consistent with multiple endocrine neoplasia, type 2A (MEN2A). Her family history was negative, suggesting that she was the clinical proband. The patient underwent a laparoscopic partial (to preserve as much adrenal tissue as possible) left adrenalectomy in March 2020.

At 1-month follow-up post pheochromocytoma resection, the patient reported complete resolution of her palpitations, neck and jaw pain, and headaches. A 24-h Holter monitor was normal without any evidence of junctional rhythm. As part of her MEN2A diagnosis, thyroid studies and thyroid ultrasound was performed, both of which were normal. Total thyroidectomy was performed in July 2020.

## Discussion

Our case illustrates a unique cardiovascular presentation of a pheochromocytoma, specifically the occurrence of junctional rhythm. While junctional tachycardia and other tachyarrhythmias have previously been described as a presenting sign of pheochromocytoma or paraganglioma in children,

junctional rhythm without tachycardia has not been reported.<sup>2-5</sup> This adolescent was noted to have junctional rhythm at the time of clinical symptoms, as captured on non-invasive cardiac monitors. There have been case reports illustrating sinus node dysfunction and junctional rhythm in an adult patient with pheochromocytoma and long-standing hypertension.<sup>6</sup> Junctional rhythm as a presenting rhythm for a pheochromocytoma has not been previously reported in the pediatric literature. This unique rhythm complication is not commonly seen in young patients with catecholamine secreting tumors.

While fractionated catecholamines were not sent to confirm, the episodic symptoms of palpitations, headache, and syncope experience as well as the elevated metanephrines may suggest an epinephrine predominate secreting pheochromocytoma.<sup>7</sup> Increased circulating catecholamine can cause heterogeneous activation of alpha, beta, and dopaminergic receptors leading to rapid variation in inotropic effects, chronotropic effects, and vascular tone changes resulting in changes in blood pressure. Initial treatment with atenolol led to the patient reporting mood swings, irritability, and worsening headaches. Atenolol is a selective beta<sub>1</sub>-receptor blocker

and may have little effect on  $\beta_2$ , and therefore, the patient's symptoms may have worsened due to the unopposed  $\alpha_1$  adrenergic receptors resulting in significant vasoconstriction. The increased circulating catecholamines leading to the patient's symptoms coupled with the unique ECG findings was nicely correlated with the exercise test which proved helpful in the evaluation and eventual diagnosis.

Exercise stress testing helped correlate symptomatic junctional rhythm events to episodic hypertension. It also provided insight to explain a pathophysiologic mechanism of the patient's clinical presentation. Throughout the EST, the patient had intermittent blood pressures that would be considered an exaggerated blood pressure response to exercise. The normal blood pressure response to dynamic exercise will cause at least a 20% increase in systolic blood pressure while causing a much smaller increase in diastolic blood pressure.<sup>8</sup> Although normal peak exercise blood pressure differs slightly among children based on gender or race,<sup>9</sup> systolic blood pressure should rarely exceed 200 mmHg in males and 180 mmHg in females.<sup>8,10,11</sup> Excessive rise in blood pressure during exercise can be a manifestation of a coarctation of the aorta,<sup>12,13</sup> but if already ruled out on echocardiogram, this finding should prompt further investigation. In this case, the excessive hypertension led to further evaluation and eventual diagnosis of a pheochromocytoma. In this case, the EST was critical in making the diagnosis by allowing us to correlate the hypertensive episodes to the junction rhythm and the patient's symptoms.

Physiologic increases in heart rate during exercise occur to augment cardiac output and subsequently oxygen delivery, due to an increase in the sympathetic activity and a reduction in the parasympathetic autonomic nervous system activity.<sup>8,14</sup> An increase in parasympathetic activity has the opposite effect. The concept of inhibitory cardiac sensory receptors has been described since the 1860s.<sup>15</sup> Well-known examples include the Bezold–Jarisch reflex and the arterial baroreceptor reflex. The baroreceptor reflex occurs in response to acute hypertension, activating stretch receptors located in the aortic arch and carotid sinus. This then results in increased parasympathetic tone, manifesting as bradycardic hypotension.<sup>16,17</sup> In this case, the patient had a normal heart rate response to exercise with a peak heart rate of 94% predicted which remained as a sinus rhythm throughout exercise, even with extremely high blood pressure.

Once exercise stopped, the heart rate (and likely sympathetic and parasympathetic input) was returning to the patient's baseline with an elevated blood pressure correlating with junctional rhythm. This would suggest that the parasympathetic input now had the predominant effect on the sinus node, resulting in a bradycardic rhythm as a result of the aforementioned arterial baroreceptor reflex. Reflex inhibition at the level of the baroreceptor may be a predominant component of the junctional rhythm, but it is important to mention that central sympathetic outflow activity can also be

altered and be playing a role as an exaggerated adrenergic response.<sup>18</sup>

Exercise stress testing proved extremely valuable as part of this patient's comprehensive work up and emphasizes the importance of performing a thorough work up in patients who have cardiac symptoms, especially during exercise. A high functioning exercise physiology lab with standardized workflows is part of that evaluation. Although testing was helpful in this case, inexperienced labs or personnel should proceed with caution as severe hypertension (>250 mmHg systolic or 125 mmHg diastolic, or blood pressure higher than can be measure by equipment) is an indication to discontinue a test or not test at all as it could lead to patient decompensation.<sup>19</sup> With the help of an EST, we can speculate that our patient's presentation of junctional rhythm was secondary to her episodic hypertension, as demonstrated during stress testing. During periods of junctional rhythm, the electromechanical dyssynchrony between atrial and ventricular contraction, along with the likely catecholamine release, resulted in her symptoms of headache, neck pain, and palpitations.

## Conclusion

Although junctional rhythm can be a normal finding during periods of higher vagal tone such as sleep, or in highly athletic individuals, symptomatic junctional rhythm should prompt additional evaluation for secondary causes. This unusual presentation illustrates the benefit of including an EST as part of a comprehensive clinical evaluation, which in this case led to the eventual diagnosis.

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## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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## Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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