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Sex Hormone Deficiency and Cardiac Conduction: A Potential Link Between Hypogonadism and Sick Sinus Syndrome

Barbora Jociutė*
Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania
E-mail: bjociute@gmail.com
ORCID ID https://orcid.org/0009-0007-4664-1400
ROR https://ror.org/0069bkg23

Milda Pociūtė
Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania
E-mail: milda.pociute@stud.lsmu.lt
ORCID ID https://orcid.org/0009-0001-2651-9797
ROR https://ror.org/0069bkg23

Indrė Čeponienė
Institute of Cardiology, Lithuanian University of Health Sciences, Kaunas, Lithuania; Heart Centre, Lithuanian University of Health Sciences, Kaunas, Lithuania
ROR https://ror.org/0069bkg23
ORCID ID https://orcid.org/0000-0003-1975-8412
E-mail: indre.ceponiene@kaunoklinikos.lt

Rasa Verkauskienė
Institute of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania; Clinical Department of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania
E-mail: rasa.verkauskiene@kaunoklinikos.lt
ORCID ID https://orcid.org/0000-0002-0108-9305
ROR https://ror.org/0069bkg23

Jonas Čeponis
Institute of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania; Clinical Department of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania
E-mail: jonas.ceponis@lsmu.lt
ORCID ID https://orcid.org/0000-0003-4261-5014
ROR https://ror.org/0069bkg23

Abstract. ***Background:*** Hypogonadotropic hypogonadism (HH) is an endocrine disorder characterized by insufficient gonadotropin secretion, leading to low testosterone levels in men and delayed or absent puberty. While primarily affecting reproductive and sexual development, testosterone deficiency may also influence cardiovascular function. This case report explores the potential interplay between HH and bradycardia.

Clinical Summary: In order to explore this potential link, we reviewed current literature on functional HH and its systemic manifestations, with particular attention to cardiovascular involvement. Additionally, we describe a clinical case encountered in our practice involving a 21-year-old male presenting with delayed puberty, marked fatigue, bradycardia, and significant weight loss. Cardiac evaluation revealed sick sinus syndrome (SSS) requiring dual-chamber pacemaker implantation, while hormonal assessment confirmed HH. Testosterone replacement therapy (TRT) was initiated, leading to full pubertal progression. Over time, the hormonal function normalized, allowing cessation of TRT without recurrence of hypogonadal symptoms – thus suggesting a reversible, functional form of HH. Findings from this case were considered alongside similar reports and physiological studies addressing androgen effects on the cardiac function.

Discussion: This case illustrates of a functional and reversible form of HH. While chronic bradycardia has not been previously reported as a cause of functional HH, the pathophysiological mechanism – namely, chronic low cardiac output, is known to impair hormonal regulation. The co-occurrence of bradycardia and

* Corresponding author

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HH suggests a link between androgen deficiency and cardiac electrical system impairment, with this link being possibly bidirectional, as supporting literature highlights the role of testosterone in cardiac repolarization and myocardial performance.

Conclusions: It is important to recognize the complexity of androgen regulation, as well as multisystemic effects of testosterone deficiency, including its potential impact on the cardiac rhythm. Conversely, in young males with unexplained bradycardia and pubertal delay, functional HH should be considered. Persistent bradycardia may itself contribute to the development of functional HH, highlighting likely a bidirectional relationship between the two diseases. Further research is therefore essential to better understand this two-way interaction and its clinical implications for both cardiovascular health and hormonal balance in younger populations.

Keywords: functional hypogonadotropic hypogonadism, sick sinus syndrome, testosterone replacement therapy.

Lytinių hormonų trūkumas ir širdies laidumas: galimas hipogonadizmo ir sinusinio mazgo sindromo ryšys

Santrauka. ***Įvadas:*** Hipogonadotropinis hipogonadizmas (HH) – tai endokrininis sutrikimas, kuriam būdingas nepakankamas gonadotropinų išsiskyrimas, dėl kurio vyrams sumažėja testosterono lygis, o mergaitėms vėluoja arba visai nepasireiškia brendimas. Nors testosterono trūkumas pirmiausia daro įtaką reprodukciniam ir seksualiniam vystymuisi, jis taip pat gali paveikti širdies ir kraujagyslių sistemos funkcionavimą. Šiame atvejo aprašyme nagrinėjama galima HH ir bradikardijos sąveika.

Klinikinis atvejis: Siekdami ištirti šį galimą ryšį, apžvelgėme naujausią literatūrą apie funkcinį HH ir jo sisteminius pasireiškimus, ypatingą dėmesį skyrėme širdies ir kraujagyslių sistemos pažeidimams. Be to, aprašome mūsų praktikoje pasitaikiusį 21 metų vyro, kuriam pasireiškė vėluojantis brendimas, ryškus nuovargis, bradikardija ir žymus svorio netekimas, klinikinį atvejį. Atlikus pacientui širdies tyrimą buvo nustatytas sinusinio mazgo sindromas (SSS), dėl kurio reikėjo implantuoti dviejų kamerų širdies stimuliatorių, o hormonų tyrimai patvirtino HH. Buvo pradėta testosterono pakaitinė terapija (TRT), po jos brendimas visiškai baigėsi. Laikui bėgant hormoninė funkcija normalizavosi, todėl buvo galima nutraukti TRT be hipogonadizmo simptomų pasikartojimo – tai rodo, kad tai buvo grįžtamoji, funkcinė HH forma. Šio atvejo duomenys buvo nagrinėjami kartu su panašiais pranešimais ir fiziologiniais tyrimais, kuriuose nagrinėjamas androgenų poveikis širdies funkcijai.

Diskusija: Šis atvejis iliustruoja funkcinę ir grįžtamąją HH formą. Nors anksčiau nebuvo pranešta, kad lėtinė bradikardija būtų funkcinės HH formos priežastis, žinoma, kad patofiziologinis mechanizmas – būtent lėtinis mažas širdies išmetamasis tūris – sutrikdo hormonų reguliaciją. Bradikardijos ir HH pasireiškimas kartu leidžia daryti prielaidą, kad yra androgenų trūkumo ir širdies elektrinės sistemos sutrikimų ryšys; šis ryšys gali būti abipusis, nes atitinkamoje literatūroje pabrėžiamas testosterono vaidmuo širdies repoliarizacijoje ir miokardo veikloje.

Išvados: Svarbu suprasti androgenų reguliacijos sudėtingumą, taip pat testosterono trūkumo poveikį kelioms organizmo sistemoms, įskaitant galimą įtaką širdies ritmui. Atvirkščiai, jauniems vyrams, kuriems pasireiškia nepaaiškinama bradikardija ir vėluoja lytinis brendimas, reikėtų įtarti funkcinį HH. Nuolatinė bradikardija pati savaime gali prisidėti prie funkcinio HH išsivystymo, o tai rodo, kad tarp šių dviejų ligų greičiausiai yra abipusis ryšys. Todėl būtini tolesni tyrimai, siekiant geriau suprasti šią abipusę sąveiką ir jos klinikinius padarinius tiek širdies ir kraujagyslių sveikatai, tiek hormonų pusiausvyrai jaunesnių žmonių populiacijoje.

Raktažodžiai: funkcinis hipogonadotropinis hipogonadizmas, sinusinio mazgo sindromas, testosterono pakaitinė terapija.

Background

The human reproductive system and the development of secondary sexual characteristics are governed by the *Hypothalamic–Pituitary–Gonadal* (HPG) axis. It involves a hormonal cascade beginning with the secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus, which stimulates

the anterior pituitary to release *Luteinizing Hormone* (LH) and *Follicle-Stimulating Hormone* (FSH) [1,2]. These gonadotropins act upon the gonads – testes in males and ovaries in females – to promote the production of sex steroids such as testosterone and estrogen, and gametogenesis. Sex hormones exert influence not only on normal sexual development or fertility, but also on the overall endocrine health.

Disruption at any level of the HPG axis may lead to various reproductive function disorders or syndromes, such as hypogonadism. In males, hypogonadism is associated with a decreased function of the testes and its reduced ability to produce androgens, including testosterone. Hypogonadism can be primary or secondary. Primary hypogonadism, which is also known as hypergonadotropic hypogonadism, is caused by a primary testicular pathology [3] that can include genetic, physical injury, inflammation or infection causes. On the other hand, disturbance at the hypothalamus or pituitary gland level may lead to secondary hypogonadism, known as central or *Hypogonadotropic Hypogonadism* (HH), which is often caused by genetic, neoplasm or infiltrative causes. Congenital HH is estimated to affect approximately 1 in 4,000 to 1 in 15,000 individuals in the general population [4,5], with a strong male predominance, occurring about four times more often in males than in females [6]. However, pituitary adenomas are the leading cause of hypopituitarism in adults and frequently result in secondary hypogonadism due to impaired hormone production affecting the HPG axis [7].

Functional HH is recognized as a temporary or reversible form of reproductive axis dysfunction, mostly due to low energy availability, chronic illness or severe psychological stress. In rare cases, HH can coexist with other health issues, including cardiovascular disorders [8]. One such condition is *Sick Sinus Syndrome* (SSS) – a disorder characterized by an abnormal sinus node function resulting in bradycardia [9]. This syndrome may present with nonspecific symptoms such as fatigue and dizziness. While SSS is most often caused by changes in the heart's electrical system itself, hormone imbalances – such as those seen in certain endocrine disorders – can occasionally influence the cardiac function [10].

This case study presents a challenging diagnostic journey involving a young male patient who presented with bradycardia and delayed puberty. Initial evaluation revealed endocrine abnormalities suggestive of HH, alongside SSS requiring pacemaker implantation. The overlap between his hormonal and heart-related symptoms brings up important questions about the possible connection between these two systems and how they might interact with each other.

Clinical Summary

We present the case of a 21-year-old man who presented to the cardiologist for a progressive general weakness, weight loss of 10 kg, and occasional swelling of the face and hands over a 1-year period. At the age of 21 he had been investigated by hematology and infectious disease specialists for the aforementioned symptoms and by a cardiologist for significant bradycardia, with a Holter monitoring HR ranging from 19 to 110 bpm, average HR 40 bpm. Electrocardiogram (ECG) demonstrated marked sinus bradycardia without evidence of ischemia but revealed episodes of atrioventricular (AV) rhythm. No loss of consciousness and no history of acute infections or fever for several years were presented. Delayed puberty was noted. He denied any history of tuberculosis, arterial hypertension, diabetes, and cancer. The patient was not taking any medication. The patient consumed alcohol only occasionally and denied smoking or recreational drug use. There was no family history suggestive of inherited sinus node dysfunction, thus making a hereditary form less likely.

His vital signs revealed a blood pressure of 80/40 mmHg and a heart rate of 29 bpm. His body temperature was 36.6°C, respiratory rate was 12 x/min, and a blood oxygen saturation of 97% on

room air was determined. His height was 173 cm and body mass index (BMI) was 21.7 kg/m^2. No murmurs or thrills were auscultated. Small submandibular lymph nodes were palpable. His abdomen was soft, nondistended, and non-tender, with normal bowel sounds and no organomegaly. No edema was observed in the legs. Lack of facial and axillary hair, as well as poorly developed secondary sexual characteristics were noted (Tanner stage of pubertal development P2-3, G2).

Outpatient tests were conducted: complete blood count (CBC) test was significant for thrombocytopenia (PLT 119*10^9/l (normal range is 150–400)), moderate anemia (RBC 3.83*10^12/l (normal range is 4.5–5.5), HGB 120 g/l (normal range is 130–175)), relative lymphocytosis (LYMp 64.7% (normal range is 20.0–44.0), absolute count 2.0*10^9/l (normal range is 1.0–4.5)); moderately elevated liver enzymes (AST 76 U/l (normal range is 0–35), ALT 169 U/l (normal range is 0–45)), negative markers for hepatitis B and C, negative anti-HIV, EBV IgG 0.55 (normal value is up to 0.19) – estimated by the specialist of infectious diseases as a previous history of infectious mononucleosis. Although EBV IgG positivity was interpreted as evidence of prior infection, EBV and other infectious agents such as Lyme disease, dengue fever, and typhoid were excluded. There were no abnormal findings in ultrasound of the upper abdomen. Despite extensive evaluation by hematology and infectious disease specialists, the etiology of the patient's systemic illness – including thrombocytopenia, anemia, and elevated liver enzymes – remained undetermined. During hospitalization, the initially observed hematological and biochemical abnormalities were partially resolved. Hemoglobin increased from 120 g/l to 137 g/l (normal range is 130–175), Hematocrit levels grew from 35.5% to 42.9% (normal range is 40.0–52.0), AST got reduced from 76 U/l to 44 U/l (normal range is 0–35), and ALT shrank from 169 U/l to 158 U/l (normal range is 0–45). Tests for Cytomegalovirus (CMV) antibodies were negative for IgM, but positive for IgG (291.8 U/ml). Both B. burgdorferi IgM and IgG antibodies were negative. Thyroid function tests were within normal limits (TSH 1.77 mU/l (normal range is 0.27–3.75) and FT4 11.7 pmol/l (normal range is 10–22)), effectively excluding hypothyroidism as a cause of bradycardia. Hormone tests results revealed low levels of testosterone at 3.29 nmol/l (normal range is 9.08–30.16), luteinizing hormone (LH) 0.5 IU/I (normal range is 1.7–11.2), and follicle stimulating hormone FSH <1 IU/I (normal range is 2.1–18.6), suggestive of hypogonadotropic hypogonadism.

Due to a diagnosed sick sinus syndrome (SSS) a Dual-chamber (DDDR) type electrical pacemaker was implanted. The dual-chamber pacemaker was implanted before the initiation of testosterone replacement therapy. Therefore, the direct effect of testosterone replacement therapy on the intrinsic sinus node function could not be assessed. During the subsequent follow-up, the patient remained clinically stable with pacemaker support. Follow-up electrocardiograms demonstrated a sinus rhythm with effective atrial pacing, with a heart rate of a preset 55 beats per minute.

After observing signs of insufficient pubertal development and a deficiency of male reproductive hormones, the patient was directed to the Endocrinology department for diagnosis and further treatment. With hormone levels remaining low on consecutive testing, based on hypogonadal symptoms (low libido or sexual thoughts, no morning erections), hypogonadotropic hypogonadism was diagnosed, and testosterone replacement therapy was initiated with testosterone undecanoate 1000mg/4ml every 12 weeks.

To further evaluate the etiology of hypogonadotropic hypogonadism, additional endocrine investigations were performed. Serum prolactin was 87 mU/l (normal range is 38–337). Assessment of the adrenal axis, including serum cortisol (571.91 nmol/l (normal range is 177–578)) and adrenocorticotropic hormone (ACTH) (5.6 pmol/l (normal range is 1.63–14.15)) did not reveal abnormalities suggestive of additional pituitary hormone deficiencies. Genetic testing was not performed because the clinical course and subsequent recovery of the gonadotropin function reduced

suspicion of a congenital form of HH. Brain magnetic resonance imaging (MRI) with dedicated pituitary imaging was not performed due to an implanted cardiac pacemaker, which precluded MRI examination at that time.

At the age of 25 years, testosterone replacement therapy was discontinued after the patient had completed pubertal development and remained clinically stable. The patient was subsequently followed for four years. During the follow-up, serum testosterone, LH and FSH levels were reassessed three times.

The pre-discontinuation trough testosterone level was 11.8 nmol/l. After discontinuation of the treatment, the testosterone level decreased to 6.7 nmol/l, FSH to 1 IU/I, and LH was 1.1 IU/I, whereas, subsequently, the testosterone levels ranged from 12.3 nmol/l to 13.83 nmol/l, LH and FSH from 2.3 IU/I and 1.9 IU/I to 1.7 IU/I and 4.7 IU/I, respectively. Despite the low-normal values, the patient presented with no hypogonadal symptoms. By this time the patient had fully gone through puberty (P5, G5) with presentation of a healthy male secondary sexual characteristic. No further hormonal replacement therapy was deemed necessary.

After the discontinuation of the testosterone replacement therapy, follow-up electrocardiography continued to demonstrate a sinus rhythm with effective atrial pacing, with a heart rate of approximately 60 beats per minute. No recurrence of clinically significant bradycardia or related symptoms was observed. The pacemaker remains *in situ* and continues to provide cardiac support.

Previously described cases of HH with partial phenotypic overlap have been reported and highlight the possible interplay between endocrine dysfunction and cardiac manifestations; however, there exist important clinical differences between the cases. For instance, Owais Rashid *et al.* (Table 1) published a case of a 34-year-old male with idiopathic HH with the complaints of absent facial, axillary and pubic hair, as well as low GnRH and testosterone levels. After nine months of testosterone replacement therapy, the patient's condition improved and following two more months after the hold of treatment, the testosterone treatment was discontinued due to the signs of recovered hypothalamic–gonadal axis and normal hormone levels (testosterone levels off replacement were 15.05 nmol/l (433.80 ng/l (normal range is 249.00–836.00)) and LH level was 3.30 mIU/mL (normal range is 1.20–7.80)) [13]. Unlike our patient, this individual had no systemic illness, weight loss, or cardiovascular involvement, thus limiting the comparability of the two cases. Also, Elena Passeri *et al.* (Table 1) published two similar cases of 65- and 30-year-olds with long-standing HH including wasting syndrome, bradycardia, and heart failure. Both patients were admitted to the emergency department with complaints of deep general weakness, anemia and severe bradycardia, in one case (65-year-old) requiring the implantation of a single chamber pacemaker for heart failure treatment. Contrary to our patient, who exhibited a normal thyroid function and therefore did not require thyroid hormone replacement, the latter two patients were started on testosterone and L-thyroxine replacement therapy, leading to significant clinical improvement; the treatment was continued for the first patient (65-year-old) due to unresolved growth hormone (GH) deficiency, thus suggesting involvement of multiple axes. In the first case, the advanced age of the patient (65 years) and the presence of multiple pituitary hormone deficiencies make it difficult to attribute cardiac disease primarily to testosterone deficiency. The second patient (who was 30-year-old) experienced a 12 kg weight gain with improvements in the muscle mass and an increase in the heart rate from 32 to 56 bpm. Notably, the improvement in heart rate coincided with substantial weight gain, suggesting that nutritional recovery may have played a significant role. Both hypothyroidism and low levels of insulin-like growth factor 1 (IGF1) resolved eventually [8].

Table 1. Overview of published cases presenting with hypogonadotropic hypogonadism and bradycardia

Clinical case authors	Data categories	Detailed data
Owais Rashid et al. (2017) [13]	Age and BMI	34-year-old male with height of 172.5 cm and a weight of 68 kg (BMI 22.85 kg/m^2).
	Laboratory tests	LH was 2.60 mlU/mL (normal limit in males: 1.2–7.8), FSH 1.50 mlU/mL (1.5–15.4), morning testosterone 1.94 nmol/l (8.64-29.01) (55.99 ng/dL (249–836)), prolactin 5.2 ng/mL (2–18), thyroid stimulating hormone (TSH) 1.03 ulU/mL (0.4–4.2) and free thyroxine (T4) 1.13 ng/dL (0.89–1.76).
	Comorbidities	No known comorbidities were presented.
	sexual characteristics/ genital development	No facial and sparse axillary, and pubic hair, bilateral gynaecomastia, stretch penile length was 5 cm and bilateral testicular volume – 10 mL. Decreased early morning erections and absent ejaculations.
	Administered treatment	250 mg testosterone injection once every 4 weeks, which was later decreased to 250 mg once every 6 weeks.
	Treatment results	After cessation of 9 months lasted testosterone replacement therapy, the patient's testicular size increased to 20 mL bilaterally, and his penile length increased to the mean adult size for his age. Testosterone and LH levels were normalized.
Elena Passeri et al. (2014) [8]		
1st clinical case	Age and BMI	65-year-old male with height of 175 cm and a weight of 83.3 kg (BMI 27.2 kg/m^2).
	Laboratory tests	Severe HH: testosterone <0.02 ng/mL; FSH 0.18 mU/mL; LH <0.1 mU/mL. Concomitant hypothyroidism: TSH 7.0 mU/L (0.4–4), freeT3 2.1 pg/ml (2.6–4.4), freeT4 0.65 ng/dl (0.9–1.7). Growth hormone (GH) deficiency: peak GH level was 1.3 ng/ml after combined stimulation with GHRH 1 μg/kg body weight + arginine 30 g; insulin-like growth factor 1 (IGF1) 25 ng/ml (117–252) and mild hyperprolactinemia: prolactin 34 ng/ml (<20).
	Comorbidities	The patient presented with lethargy and had been bedbound for a few days, with progressive physical deterioration over the past year. Heart failure due to severe bradycardia (27 bpm), mild hypokinetic cardiomyopathy, third degree atrioventricular block and anemia (hemoglobin 7.2 g/dl (12.0–15.0) were observed. Elephantiasis, caused by chronic lymphedema, was noted.
	sexual characteristics/ genital development	Feminine appearance: female body fat distribution, high-pitched voice and eunuchoidal body proportions (height 175 cm, arm span 177 cm, BMI 27.2 kg/m^2). Minimal body hair, mild gynecomastia and underdeveloped scrotum, microphallus and bilateral cryptorchidism.
	Administered treatment	Testosterone and L-thyroxine replacement therapy.
	Treatment results	After six months of therapy: mild masculinization, weight gain (+7 kg) and resolution of anemia, but central hypothyroidism and GH deficiency did not resolve (TSH 0.08 mU/L, freeT4 0.83 ng/dl, IGF1 25 ng/ml).

Clinical case authors	Data categories	Detailed data
2nd clinical case	Age and BMI	30-year-old male with BMI of 19 kg/m^2.
	Laboratory tests	Severe HH: testosterone 1.3 ng/ml (2.4–10.0), LH 0.6 mU/ml, FSH 1.1 mU/ml. Mild hypothyroidism: TSH 5.5 mU/L, freeT3 1.7 pg/ml (2.6–4.4), freeT4 0.8 ng/dl (0.9–1.7). Low IGF1 level of 107 ng/ml (117–252), normal adrenal function.
	Comorbidities	Hypotension, deep bradycardia (32 bpm), fatigue and anemia. The patient complained of low sexual desire and erectile dysfunction, experienced 19 kg weight loss in the previous year. Fainting episodes once a week, progressive diffuse myalgia, anxious-depressive disorder and neurosensorial hypoacusia resulting from infantile measles meningitis.
	sexual characteristics/ genital development	Testes small and soft in the scrotum, volume 5 ml, while external genitalia were normal.
	Administered treatment	testosterone and L-thyroxine replacement therapy.
	Treatment results	After six months of treatment, there was a significant improvement in the overall well-being: the patient gained 12 kg in weight with an improvement of the muscle mass, heart rate (56 bpm) and IGF1 levels getting normalized. Hypothyroidism resolved, and L-thyroxine replacement therapy was discontinued.

Discussion

During late adolescence and early adulthood – that is, when testosterone production typically peaks – sex hormones deficiency can be associated with widespread disorders and symptoms. Here, we report a case of a young man experiencing delayed puberty and deep bradycardia. Although a dual-chamber pacemaker was implanted prior to initiating testosterone replacement therapy, thereby precluding direct observation of the hormonal impact on the heart rate, the subsequent normalization of gonadotropin and testosterone levels following the cessation of therapy suggests a reversible, functional form of HH. In the clinical practice, the most frequent cause of delayed puberty is constitutional delay of growth and puberty (CDGP), which is, usually, a familial physiological self-limited condition, mostly resolving by 18 years of age. Due to the common isolated presentation, the most frequent differential diagnosis of CDGP is HH that may be either organic (acquired or congenital) or functional due to central suppression of the hypothalamic-pituitary-gonadal axis after puberty has begun or should have begun, usually due to a chronic illness, stress, energy deficiency, excessive physical exertion [11,12]. In our patient, no family history of CDGP was present, and pubertal development started spontaneously with subsequent arrest at around 21 years, suggesting functional HH as a most likely condition.

However, the interplay between testosterone deficiency and cardiovascular dysfunction is multifaceted and significant. Among the various cardiac manifestations linked to hypogonadism, QT interval prolongation is particularly noteworthy. A prolonged QT interval increases the risk of developing serious arrhythmias, such as torsades de pointes (TdP), which can progress to sudden cardiac death [14]. For example, a pilot study involving 26 men with primary or secondary hypogonadism revealed that four had prolonged QT intervals. Moreover, after starting the testosterone replacement

therapy (TRT), their QT intervals normalized, thus suggesting the relevance of testosterone in keeping a stable electrical activity of the heart [15]. In several studies, the effects of the testosterone replacement therapy were investigated including not only patients with a prolonged QT interval, but also with heart failure (HF). A meta-analysis of randomized controlled trials involving male patients with both HF and hypotestosteronemia revealed that while TRT did not produce significant changes in the left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, or mortality, it was linked to notable increase in heart rate and insulin sensitivity [16]. Further supporting these findings, a systematic review of randomized controlled trials by Theodorakis et al. showed the effects of TRT in testosterone-deficient men with HF. Although the systematic review did not find major improvements in the blood pressure or lipid profiles, TRT was associated with significant improvements in the muscle strength, aerobic capacity, and insulin sensitivity, as well as shortening of the QT interval, indicating a positive effect on cardiac electrical stability [17].

Despite these findings, the relationship between testosterone, cardiac health, and TRT has been controversial. Observational and clinical trial data have raised concerns about potential cardiovascular risks associated with TRT, particularly regarding atherosclerotic plaque progression and vascular remodeling. Notably, a substudy of the Testosterone Trials demonstrated that, in older hypogonadal men (≥65 years), 12 months of TRT led to a significantly greater increase in non-calcified coronary artery plaque volume compared to placebo (from median values of 204 mm^3 to 232 mm^3 vs. 317 mm^3 to 325 mm^3, respectively; estimated difference, 41 mm^3; 95% CI, 14 to 67 mm^3; $p = 0.003$) [18]. This finding raised concerns about a possible pro-atherogenic effect of exogenous testosterone, particularly in men with pre-existing cardiovascular risk factors.

More definitive insights emerged from the TRAVERSE trial – a large, multicenter, randomized controlled trial involving 5246 men aged 45–80 years with documented hypogonadism and an increased cardiovascular risk. This landmark study found that TRT was noninferior to placebo regarding the incidence of major adverse cardiovascular events (MACE) (7.0% vs. 7.3%, hazard ratio 0.96; 95% CI, 0.78–1.17; $p < 0.001$ for noninferiority), effectively alleviating earlier concerns about overt cardiovascular harm from testosterone therapy [19].

Our case, alongside previously reported instances, hypothesizes the complex relationship between testosterone deficiency and cardiac disorders. Several mechanisms have been proposed to explain how testosterone can affect cardiac function. The current literature shows that testosterone shortens the QT interval by enhancing potassium (K^+) currents and suppressing calcium (Ca^{2+}) currents, thereby accelerating cardiac repolarization [20]. It influences both cardiac contractility and relaxation, playing a significant role in the myocardial performance [21]. In rat cardiomyocytes, testosterone reversed the hypocontractility caused by castration [22]. Moreover, literature indicates that it functions as a positive inotropic agent through activation of androgen receptors (AR) in animal cardiac myocytes [23]. Another mechanism that could explain cardiac myocyte contractile dysfunction related to low testosterone levels is linked to oxidative stress, which may impair the ability of interfibrillar mitochondria (IFM) to effectively produce and deliver ATP to the muscle filaments responsible for contraction [24]. Furthermore, testosterone has been found to exert cardioprotective effects via intracellular pathways, including regulation of apoptosis [25], modulation of reactive oxygen species (ROS) production [26], and activation of the nitric oxide (NO)–cyclic GMP pathway [27]. Such mechanisms may contribute to maintaining myocardial integrity and preventing bradycardia in the presence of adequate testosterone levels.

Chronic illness, including heart failure (HF), is frequently associated with reduced testosterone levels [11,12,28]; however, it remains unclear whether testosterone deficiency is a cause or a consequence of systemic disease and poor nutritional status. In patients with chronic disease, cachexia frequently coexists with hypogonadism, and both share overlapping clinical features such

as low lean body mass, fatigue, and poor quality of life, suggesting that reduced testosterone levels may be a consequence of the catabolic milieu and poor nutritional status rather than an isolated primary endocrine disorder. Tabei *et al.* highlight that cachexia occurs alongside hypogonadism in chronic disease states and that testosterone therapy can increase lean body mass and energy levels, although data are mixed and causality remains unresolved [29]. Moreover, recent literature on the pathophysiology of cachexia emphasizes that this multifactorial wasting syndrome is characterized by systemic metabolic disturbances and hormonal imbalances – including disruptions in anabolic-catabolic signaling and endocrine axes – which contribute to muscle loss and reduced anabolic hormone levels such as testosterone, underscoring that low testosterone in chronic illness may reflect broader cachectic processes rather than isolated primary gonadal dysfunction [30].

The underlying cause of functional HH in our patient remains uncertain. Several factors may have contributed to suppression of the hypothalamic–pituitary–gonadal axis. The patient presented with substantial weight loss, severe bradycardia, hypotension, anemia, thrombocytopenia, and elevated liver enzymes, suggesting a significant systemic illness and possible reduced energy availability. Both systemic illness and inadequate energy availability are recognized factors that may suppress reproductive axis activity. In addition, severe persistent bradycardia may have resulted in reduced cardiac output and could potentially have contributed to impaired hypothalamic–pituitary–gonadal axis function. However, the available data do not allow us to determine whether cardiac dysfunction preceded hypogonadism, whether hypogonadism contributed to the cardiac phenotype, or whether both conditions resulted from a common underlying systemic process. Therefore, the proposed association between severe bradycardia and functional HH should be considered a hypothesis rather than a demonstrated causal relationship.

The effects of severe chronic cardiac disease on delayed puberty as a sign of functional hypogonadism have been documented in Fontan procedure survivors, a population known to experience chronic low cardiac output [31, 32]. Thus, although chronic bradycardia has not been previously reported as a cause for functional hypogonadotropic hypogonadism, it potentially shares the same pathogenetic mechanism of chronic low cardiac output that is known to precipitate this hormonal dysfunction.

Conclusions

This case suggests a possible association between functional hypogonadotropic hypogonadism (HH) and severe cardiac conduction abnormalities in a young man. However, the presence of significant systemic illness, weight loss, hypotension, and severe bradycardia makes it difficult to establish a direct causal relationship between testosterone deficiency and sick sinus syndrome (SSS). Functional HH may have been associated with the patient's overall systemic condition and reduced energy availability, while the contribution of cardiovascular dysfunction remains uncertain. Therefore, the relationship between cardiac dysfunction and functional HH cannot be determined from this case alone and remains hypothetical. Further studies are needed to clarify this relationship, particularly in adolescents and young adults.

Author contributions

B. J.: Conceptualization, Data Curation, Visualization, Writing – Original Draft Preparation.
M. P.: Visualization, Writing – Original Draft Preparation.
I. Č.: Conceptualization, Resources, Supervision, Validation, Writing – Review & Editing.
R. V.: Supervision, Validation, Writing – Review & Editing.
J. Č.: Conceptualization, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Review & Editing.

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