

CASE REPORT

Linear and Nonlinear Heart Rate Variability Analysis in Gonadal Dysgenesis (Swyer Syndrome): A Case Report

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Abstract

Swyer syndrome is one of the disorders of sexual differentiation. Previous studies have demonstrated increased sympathetic activity with heart rate variability (HRV) analysis with decreasing estradiol levels. One patient presented a pure 46, XY gonadal dysgenesis with female phenotype. Cardiac autonomic modulation was assessed through HRV analysis while at rest. This research analyzed linear and nonlinear indexes. HRV analysis showed reduced parasympathetic and global modulation with an apparent increase in sympathetic tone and a loss of HR fractal dynamics toward correlated behavior, characterized by low entropy and high determinism of time series.

Introduction

Swyer syndrome is one of the disorders of sexual differentiation (DSD), a pure gonadal dysgenesis with karyotype 46, XY, the presence of two digenetic gonads or gonads streak, and devoid of germinative elements. The clinical presentations are female phenotype with typical female external genitalia, primary amenorrhea and persistent hypergonadotropic hypogonadism, normal stature, and absence of somatic malformations.¹

Previous studies have demonstrated increased sympathetic activity with heart rate variability (HRV)

Keywords

Autonomic Nervous System; Estrogen, Replacement Therapy; Amenorrhea; Gonadectomy; Heart Rate; Cardiovascular Diseases/complications.

analysis with decreasing estradiol levels. However, the clinical and therapeutic implication of autonomic impairment is still unclear.¹ This study reports on the autonomic behavior of HRV in Swyer Syndrome, but the report exempts itself from an in-depth review.

Case Report

A 48-year-old married Brazilian woman participated in this research in the Endocrine Gynecology and Menopause Clinic the São Paulo University Medical School. Patient follow-up began in 1983, at which time the patient received a diagnosis of gonadal dysgenesis in her adolescence. This case report was approved by the ethics committee of the *Faculdade de Medicina da Universidade de São Paulo* (FMUSP) (Protocol n° 2.368.076), and the patient's anonymity and consent were guaranteed.

After the primary amenorrhea diagnosis, followed by the gonadal dysgenesis diagnosis, the patient was treated with estradiol valerate and levonorgestrel (2mg+0.25mg)/day. At age 21, she went through a bilateral oophorectomy procedure. She reported no other hospitalizations, pre-existing diseases, or use of other regular medication. Her gynecological examination showed female genitalia with trophism and pubic hair development, both age-appropriate, and no injuries.

She reported no chronic or infectious gynecological diseases. She denied alcohol or drug abuse, but had a history a smoking. The general physical examination showed good general condition, ruddy, hydrated, afebrile, respiratory rate of 19/min, normal blood pressure, body mass index of 33.33 kg/m². Cardiac, pulmonary, abdominal, and biochemical exams showed no relevant findings.

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Cardiac autonomic modulation was assessed through HRV analysis. RR interval recordings were obtained by a validated heart rate receiver,² placed on the chest, with the patient at rest for 20 min. HRV analysis was performed as proposed by Godoy et al.,³ using linear (time and frequency domains) and nonlinear methods.⁴ Additionally, geometric indexes, Poincaré and recurrence plots, entropy-based techniques, and Detrended Fluctuations Analysis⁵ (DFA) were analyzed (Table 1).

Discussion

This study found signs of reduced parasympathetic and global modulation with an apparent increase in the sympathetic tone and a loss of HR fractal dynamics toward correlated behavior, characterized by low entropy and high determinism in a time series.

Our study subject had been using hormonal therapy (HT) (natural estrogen and second-generation progestogen) since having been diagnosed with amenorrhea. Previous studies^{1,6} have evaluated the effect of sex hormones and distinct interventions on cardiac

autonomic modulation. It is known that menopausal women present a lower HRV when compared with women who are not in menopause,⁶ and that HT⁷ and exercise⁸ can apparently improve cardiac autonomic modulation. Liu et al.,⁹ investigated the role of estrogen in gender-related autonomic differences and found that during the postmenopausal period, the vagal and sympathetic activities were lower and higher, respectively.

Effects of oophorectomy on cardiac autonomic modulation revealed an imbalance in the regulation of the cardiovascular system, with a decrease in cardiac vagal modulation and an increase in sympathetic activity.¹⁰ Since our patient underwent a bilateral oophorectomy procedure, this case report also incorporates important endocrine features, which, along with genetic features, were both important to understand the modification of cardiovascular risk.

In linear methods, we found lower parasympathetic indices (RMSSD and HF) than the mean values of previous studies.¹ LF and LF/HF were higher, which could be related to an increase in the sympathetic tone.^{4,5} SDNN, which presents global modulation, was lower

Table 1 – HRV linear and nonlinear indices of the Swyer Syndrome patient.

| Linear methods | | Nonlinear methods | |
|-----------------------|-------|-------------------|-------|
| Time domain | | Recurrence plot | |
| Mean RRi (ms) | 722.1 | | |
| SDNN (ms) | 21.3 | | |
| Mean HR (1/min) | 83.16 | | |
| RMSSD (ms) | 9.5 | Lmean (beats) | 16.37 |
| <i>Geometrics</i> | | Lmax (beats) | 988 |
| RR tri | 6.711 | REC (%) | 41.30 |
| TINN (ms) | 105.0 | DET (%) | 99.43 |
| SD1 (ms) | 6.7 | ShanEn | 3.668 |
| SD2 (ms) | 29.3 | | |
| SD1/SD2 | 0.228 | | |
| Frequency domain | | Other | |
| LF (ms ²) | 118 | ApEn | 1.226 |
| HF (ms ²) | 19 | SampEn | 1.227 |
| LF (nu) | 86.1 | DFA alpha1 | 1.416 |
| HF (nu) | 13.9 | DFA alpha2 | 1.007 |
| LF/HF | 6.191 | alpha1/alpha2 | 1.406 |

RRi: RR interval, SDNN standard deviation normal-to-normal intervals, RMSSD root mean square of successive differences, LF low frequency, HF high frequency, nu: normalized units. RRtri: triangular index, TINN: RRi triangular interpolation, SD1: standard deviation of the instantaneous variability in continuous RRis, SD2: standard deviation of long-term continuous RRi. SD1/SD2: ratio between short and long variations of the intervals. Lmean: Mean line length; Lmax: Max line length; REC: Recurrence rate; DET: Determinism; ShanEn: Shannon Entropy. ApEn: Approximate entropy; SampEn: Sample entropy; DFA: Detrended fluctuation analysis.

than the mean values of the same studies, which could be due to reduced parasympathetic activity.^{4,5}

As no specific studies about Swyer Syndrome with geometric and nonlinear indexes were found, our results have been compared with those from a menopause study⁸ with a similar HT. All of this study's geometric indexes, both parasympathetic (SD1) and global indexes (RRtri, TINN, SD2 and SD1/SD2), were reduced. Regarding nonlinear indices, the present study shows higher values. In the DFA analysis, values close to 1.5 are associated with signs of strongly correlated behavior,⁵ while our results pointed to a strongly correlated behavior with possible loss of fractal properties. Autonomic conditions characterized by sympathetic predominance or by the reduction in global modulation often present a correlated behavior and decrease in complexity.⁵

Sample Entropy is used to evaluate the complexity of the physiological time-series signals. Approximate Entropy is applied to quantify the amount of regularity fluctuations upon time-series data and is linked with vagal modulation and HF. Higher values indicate more complex data. Shannon entropy quantifies the degree of complexity of the signal's sample distribution. In physiological conditions, where there is a loss of time series complexity, the recurrence of points in the system increases. Their diagonals, such as Lmean, express the similarity of system behavior in two distinct time sequences.⁵ In our patient, in general, nonlinear indices showed a loss of HR fractal dynamic toward correlated behavior, characterized by low entropy and high determinism in the time series. REC and DET values were very similar to linear pattern values, typical of reduced complexity.¹¹

Our results were then compared with those from Rismini et al.,¹² who evaluated the sympathovagal balance in transsexuals. Their data demonstrated that male-to-female transsexuals (a supposedly similar genetic condition, XY, with HT) displayed significantly lower sympathetic and parasympathetic activities than did the controls, which could be mediated by the effect of hexogen estrogens, since these subjects do not have other protective factors.

To the best of our knowledge, this is the first study in the literature describing HRV nonlinear indices in Swyer Syndrome. However, this study has some limitations. First, because this is a case report, there are limitations regarding comparisons with previous literature. Secondly, it is possible that the individual's BMI and smoking history could alter the HRV parameters. Nevertheless, our study findings point out possible negative effects of

hypoestrogenism, gonadectomy, and aging in subjects with DSD, as well as the importance of HT to improve autonomic regulation during one's lifetime.

Conclusion

HRV analysis in Swyer syndrome showed reduced parasympathetic and global modulation with an apparent increase in sympathetic tone and a loss of HR fractal dynamic toward correlated behavior, characterized by low entropy and high determinism in a time series. Our findings suggest that individuals with Swyer syndrome may have increased cardiovascular risk despite HT.

Author Contributions

Conception and design of the research: VX Pereira, ICE Sorpreso. Acquisition of data: VX Pereira, AR Norbeto. Analysis and interpretation of the data: TD Carvalho, VE Valenti. Statistical analysis: TD Carvalho, VE Valenti. Writing of the manuscript: MA Marinovic Junior e JM Soares Júnior. Critical revision of the manuscript for intellectual content: ICE Sorpreso.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Faculdade de Medicina da Universidade de São Paulo* (FMUSP) under the protocol number 2.368.076. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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