Research Article

The Potential Association Between Poor Semen Quality And Cardiac Autonomic Dysfunction

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ARTICLE INFO                           ABSTRACT

Introduction: Infertility is a condition with psychological, economic, medical implications resulting in stress and trauma. Men's reproductive health is deteriorating due to deleterious environmental pollutants as well as physical and mental stress. Aims & Objectives: 1. To analyze semen and heart rate variability (HRV) in young adult males. 2. To study the correlation between semen quality and HRV in adult males. Settings and Design: Tertiary care hospital-based retrospective cross-sectional comparative study. Material & Methods: Male partners of infertile couples were investigated for semen analysis as well as HRV. Two hundred-seven infertile males and thirty healthy fertile males participated. Semen sample and all its parameters were evaluated following the recent WHO guidelines 2010 and five-minute short-term HRV was measured utilizing Power Lab/ECG Analysis Add‐On for LabChart 8. Results: The infertile males had lower semen variables than the fertile males (p<0.05 for all comparisons). Most HRV indices (time-domain and frequency-domain parameters) were lower in infertile males indicating sympathovagal imbalance among infertile males. A Spearman correlation test was applied to detect the correlation between semen parameters and HRV indices. Among the infertile males, it was observed that liquefaction time correlated significantly with SDNN (Spearman’s rho. r= 0.152, p=0.029), RMSSD (r=0.138, p=0.048) and NN50 (r=0.145, p=0.037). Sperm motility correlated significantly with HF power ms2 (r=120, p=0.046). Sperm agglutination correlated significantly with NN50 ms (r=0.086, p=0.0217). Seminal leukocytes correlated significantly with HF ms2 (r=0.131, p=0.049). Conclusion: Overall, it was found that a population with poor sperm quality affect negatively cardiac autonomic modulation in the form of decreased HRV which is an early indicator of cardiac autonomic dysfunction. Tracking HRV may be a great gold standard tool to motivate awareness of infertility-related stress or stress-related infertility. It is helpful for early intervention and maintenance of reproductive health. By actively modifying lifestyle behaviours, men can control their own fertility potential.

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INTRODUCTION:
According to the World Health Organisation (WHO), one in every four couples in developing countries is affected by infertility or subfertility problems. Worldwide about 60–80 million couples are suffering from infertility every year, out of which 15 to 20 million (25%) are in India alone.[1],[2] According to the 2013 report by WHO and the United Nations Environment Programme, since world war two the production and exposure to environmental chemicals that could disrupt the endocrine system have increased enormously.[3] Stress is associated with variations in the autonomic activity that disrupt homeostatic functions of the body therefore many researchers are studying the effects of stress on the reproductive health. Infertility or subfertility has a major public health impact and affects a significant proportion of humanity, therefore it is a serious health issue globally which affect approximately 10% - 12% of couple worldwide.[4],[5] Globally, approximately five million children are born with In Vitro Fertilisation (IVF) therefore infertility has been known to be stressful for parents of children born with IVF. The physical or mental stress caused by harmful stimuli can affect reproductive function and such long-term stress is believed to negatively impact fertility.[6] A study done by Jacky Boivin et. al explained that women seeking medical help for infertility problems are under very much stress and require potential need and demand for infertility medical care, therefore, stress is an additional risk factor for idiopathic infertility.[7],[8] However, the extent and severity of the effects of stress on human testes are difficult to study and data mostly come from animal models. Despite this limitation, stress as a causative factor in male infertility cannot be ignored, and such patients should be made aware of its effects on testicular function and fertility which will help them to manage stress and maintain the fertility.

Heart Rate Variability (HRV) is helpful to assess Autonomic Nervous System (ANS) balance, to assess the level of physical fitness and stress coping ability, to evaluate the treatment effectiveness and prognosis.[9],[10] The ANS responds to the needs of the internal viscera as well as external stimuli. Homeostasis is associated with the regulation of internal viscera, whereas the stress response prioritizes external stimuli over internal needs. Thus, stress occurs when an organism’s physiological demands are no longer adequately fulfilled by the peripheral nervous system. Consequently, the measurement of parasympathetic tone may serve as an index of stress and stress vulnerability. Therefore, impaired reproductive health is linked to sympathovagal imbalance, which is ultimately related to heart rate variability. During chronic stress, the sympathetic nervous system is hyperactivated, causing physical, psychological, and behavioural abnormalities.[10]

MATERIAL AND METHODS:
Study design:
It is a record based retrospective cross-sectional comparative study.

Study Area and Population:
Males of the infertile couples referred to tertiary care hospital.

Study subjects and sample size:
All males among the infertile couples referred from various clinical departments to the andrology laboratory for semen analysis were included in the study.

In this record based cross-sectional study the participants with poor semen quality were included in the (i) infertile male group and the remaining participants with good semen quality were included in the (ii) fertile male group. After completion of the study, the power was calculated (using agglutination variable) to be 99.6% using open epi version 3.2

Inclusion criteria: males referred to andrology laboratory from various clinical departments for semen analysis with the age group of 20-45 years.

Exclusion criteria: The participants with any disorders of the reproductive system, taking any drug/medication/nutritional supplements which are known to affect cardiac autonomic functions, smokers, alcoholic, and drug addicts, the participants with known sleep disturbances were excluded from the study.
As mentioned above out of 237 male participants (i) 207 males were found with infertility problems so included in the infertile male group and the remaining (ii) 30 males with good semen quality were categorised under fertile male group.

**Study period:**
The study was carried out from April 2019 to March 2020.

**Data collection and ethical clearance:**
The study complies with the “National Ethical Guidelines for Biomedical and Health Research Involving Human Participants 2018” of the Indian Council of Medical research. The study had approval from the Institutional Ethical Committee of AIIMS Patna vide letter no. AIIMS/Pat/IEC/2020/484. Written consent was taken from each participant as per above mentioned national guidelines. Participant’s detailed history was taken on arrival to the andrology lab including the basic demographic, socioeconomic status, and infertility-related questions. The participant was sent to the autonomic lab to measure short term HRV. Next to it, the participant was sent to semen collection room to collect the semen for its analysis. Each study participant was given one identity number. Thus, data collected was coded with to conceal the participant’s identity before entry in the excel sheet. The data so collected was double entered in the excel sheet and compared to check for any error. Finally, the data so collected was divided into two study groups as described above.

**Semen analysis:**
Semen samples of all study participants were obtained by masturbation maintaining abstinence period of two–seven days. The semen sample obtained was analyzed for volume, pH, agglutination, liquefaction time, viscosity, sperm concentration, motility, vitality, leukocytes, and morphology. All these semen parameters were evaluated following the WHO guidelines 2010.[11]

**Heart rate variability (HRV):**
HRV is a measure of beat-to-beat temporal changes in heart rate and provides indirect insight into the ANS and further it can be used to assess sympathetic and parasympathetic balance. We studied the quality of semen and HRV in both the study groups.

**Heart rate variability analysis:**
Power lab instrument version seven (ADInstruments Ltd) had been used to record the short-term HRV of the study participants for five minutes. HRV analysis was done in detail including its time domain and frequency domain variables.

**Time-domain variables:**
It measures variations in HRV over time and the interval between successive normal cardiac cycles. SDNN: Standard deviation of NN or RR cycles, it is one of the simplest time-domain analysis intervals. It is an index of physiological resilience against stress. It is computed directly from the NN interval. It casts the overall parasympathetic and sympathetic influences on HRV. RMSSD: it is the root square of the mean of the sum of the squares of differences between successive NN intervals. It is one of the slow-changing components of HRV. pNN50: it is the percentage of NN50, it is the number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording. It directly correlated with the variability of the heart and its adaptive capacity. TP: Total Power, it determines the variance of NN intervals over the temporal segment.[12]

**Frequency-domain variables:**
It provides information about how power is distributed i.e. the variance as a function of frequency which allows the autonomic balance to be quantified at any given time. LF: Low Frequency, it corresponds mainly to the sympathetic tone along with some contribution from the parasympathetic nervous system. HF: High Frequency, it is modulated by the parasympathetic nervous system. LF/HF ratio: it is an index of the sympathovagal balance.[13]

**Statistical analysis:**
Data were analyzed using Microsoft Excel and SPPS software for windows version 20.0. Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements were presented as Mean ± SD. A student’s unpaired t-test had been used to find the significance of study parameters that were normally distributed. Mann-Whitney test had been used to find the significance of study parameters that were not normally distributed. A Spearmen correlation test was applied to detect the
correlation between semen parameters and HRV indices. Significance was assessed at p-value <0.05.

**RESULTS:**

Table 1. presents the study involved 237 men, aged 20–45 years. Depending on the semen quality data collected was divided into two groups: (i) Infertile males (N=207) with poor semen quality and (ii) Fertile males (N=30) with good semen quality. The semen variables differed between these two study groups, with the age, semen volume, pH, agglutination, liquefaction time, viscosity, sperm count, motility, vitality, leukocytes, and percentage of normal spermatozoa in the fertile men as compared to infertile males.

The significant differences in the semen parameters were observed between the infertile and the fertile males (all p values <0.05).

Table 1. Comparison of semen parameters between the two study groups

<table>
<thead>
<tr>
<th></th>
<th>Infertile males (N=207)</th>
<th>Fertile males (N=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)*</td>
<td>32.54 ± 5.42</td>
<td>30.37 ± 5.86</td>
<td>0.043</td>
</tr>
<tr>
<td>Volume (ml)*</td>
<td>2.29 ± 0.84</td>
<td>2.93 ± 0.53</td>
<td>0.0001</td>
</tr>
<tr>
<td>pH (7.2-8)*</td>
<td>7.33 ± 0.429</td>
<td>7.92 ± 0.265</td>
<td>0.0001</td>
</tr>
<tr>
<td>Agglutination (grades)*</td>
<td>2.21 ± 0.997</td>
<td>1.6 ± 0.621</td>
<td>0.001</td>
</tr>
<tr>
<td>Liquefaction time (min)**</td>
<td>40 (30-70)</td>
<td>30 (25-30)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Viscosity (cm)**</td>
<td>2.0 (1-5)</td>
<td>2 (1.75-2)</td>
<td>0.063</td>
</tr>
<tr>
<td>Sperm count (10⁶/ml)**</td>
<td>23.0 (9.8-31)</td>
<td>64 (36-79.35)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Motility (%)**</td>
<td>43 (35-47)</td>
<td>68 (57.5-74.25)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Vitality (%)**</td>
<td>31 (11-46)</td>
<td>59.8 (56-70)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Leukocytes (%)**</td>
<td>3 (2-5)</td>
<td>2 (1-2)</td>
<td>0.020</td>
</tr>
<tr>
<td>Morphology (%)**</td>
<td>14 (9-18)</td>
<td>46 (27.75-70)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Comparison of semen parameters between infertile and fertile males with P-value, p value <0.05 considered significant. *Normally distributed: expressed as mean±SD,**

**Not normally distributed: expressed as median (IQR)**

Table 2. presents the clinical data and comparison between HRV parameters of the two study groups. Regarding short-term HRV, it was observed that the marker of overall variability of the time domain range such as SDNN was significantly lower in the infertile males as compared to fertile males, while the markers of frequency domain LF power (ms²) and LF (nu) were increased in infertile males. There was a significant difference in the frequency domain of LF (nu) power indicating increased sympathetic activity among infertile males compared to fertile males. However, all parasympathetic domain parameters were significantly lower in infertile males as compared to that of fertile males. The LF/HF ratio was decreased in infertile males as compared to the fertile males representing the overall increased sympathetic activity in the infertile males.

Table 2. Comparison of HRV indices between the two study groups

<table>
<thead>
<tr>
<th></th>
<th>Infertile males (N=207)</th>
<th>Fertile males (N=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markers of sympathetic activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN (ms)**</td>
<td>35.95 (24.58-48.84)</td>
<td>41.15 (31.68-53.61)</td>
<td>0.074</td>
</tr>
<tr>
<td>LF (ms²)**</td>
<td>371.5 (167.1-714.3)</td>
<td>319.4 (188.6-689.5)</td>
<td>0.765</td>
</tr>
<tr>
<td>LF (nu)*</td>
<td>60.7 ± 20.22</td>
<td>41.29 ± 9.01</td>
<td>0.0001</td>
</tr>
<tr>
<td>Markers of parasympathetic activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMSSD (ms)**</td>
<td>23.54 (12.97-38.49)</td>
<td>31.52 (25.45-46.92)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Table 3. Among the infertile males, it was observed that liquefaction time correlated significantly with SDNN (Spearman’s rho. \( r = 0.152 \), \( p = 0.029 \)), RMSSD (\( r = 0.138 \), \( p = 0.048 \)) and NN50 (\( r = 0.145 \), \( p = 0.037 \)). Sperm motility correlated significantly with HF power \( \text{ms}^2 \) (\( r = 0.120 \), \( p = 0.046 \)). Sperm agglutination correlated significantly with NN50 ms (\( r = 0.086 \), \( p = 0.0217 \)). Seminal leukocytes correlated significantly with HF \( \text{ms}^2 \) (\( r = 0.131 \), \( p = 0.049 \)).

**DISCUSSION:**

Male infertility accounts for 40-50% of infertile couples. Approximately 42% of the men from the general population had sperm concentrations below 35 million/ml.\(^{[14]}\) Infertility itself is stressful, due to social pressures, testing, diagnosis, treatments, failures, and unfulfilled desires, and even economic costs with which it is associated. Just like earlier studies done about female infertility by Ilacqua A. et. al and Kumar N et. al among the infertile males; semen parameters may be potentially linked to stress, whose presence may reduce luteinizing hormone (LH) and testosterone pulsing, thus reducing spermatogenesis and sperm quality.\(^{[5],[15]}\)

Psychological factors such as depression, anxiety, and stress-induced changes in heart rate and cortisol levels are predictive of a decreased probability of achieving a viable pregnancy. The study carried out by J. Cwikel and et. al hypothesized three types of relationships that have been hypothesized between psychological factors and infertility. These include: (1) psychological factors are risk factors of subsequent infertility; (2) the experience of the diagnosis and treatment of infertility causes further psychological
distress; (3) a reciprocal relationship exists between stress factors and infertility. Study done by Darbandi M et al. suggested that stress associated with the workplace, family, and other factors may have adverse effects on semen quality. Long-term stress can depress testosterone and, thereby, interfere with spermatogenesis.

HRV is one of the recent non-invasive electrophysiological tools to understand the complex mechanism of autonomic homeostatic adaptation including physical and psychological challenges. HRV is a useful tool for the detection of sympathetic-parasympathetic balance in the ANS. It is strongly associated with the autonomic nervous regulatory mechanisms which in turn regulate most organ systems of the human body including cardiovascular, gastrointestinal, genitourinary systems, etc. HRV reflects as much the state of the heart as the state of the brain. Increased variability is usually seen as associated with a good health condition, whereas lowered variability might signify pathological changes. Over the past few decades, research studies have shown a relationship between low HRV and worsening mental and physical stress, a low HRV is even associated with an increased risk of diseases and death.

In our study, we observed infertile males (poor semen quality) had increased sympathetic tone compared to the healthy fertile males indicating infertile males were more stressed, the underlying reason may be environmental or psychological stressors present may impact the hypothalamic-pituitary-adrenal axis, which may affect infertile male’s HRV.

Gonadotropin-Releasing Hormone (GnRH), which stimulates the pituitary gland to produce the peripheral hormones, Luteinising Hormone (LH) and Follicle Stimulating Hormone (FSH), which in turn stimulate the production of testosterone, estradiol and sexual behaviour. Stress makes the adrenal gland produce glucocorticoids, which act directly on the hypothalamus to suppress GnRH production and stimulate Gonadotropin-Inhibiting Hormone (GnIH) production. GnIH production lower pituitary secretion of sex hormones, thereby suppressing the entire reproductive system.

An animal study carried out by Peng Zou and et al. proposed a model for stress-induced spermatogenesis impairment. A proposed molecular mechanism for the stress-induced decrease of sperm concentration in the rat epididymis involves two parts: (i) stress activates GR signalling due to increased levels of glucocorticoids, which then induces spermatids apoptosis via upregulating BAX, p53, and cleaved CASPASE 3 and (ii) stress inhibits cell cycle progression of spermatogonia at the G0/G1 phase by downregulation of CDK4, CYCLIN D1, and p-RB. Both of these two aspects explained the decreased number of spermatids in response to stress, leading to reduced epididymal sperm concentration. The animal study carried out by Daniel Filipe Cruz and Margarida Fardilha proposed that excessive nitric oxide produced during stress has been shown to damage sperm ATP. Excessive nitric oxide leads to the formation of peroxynitrite (ONOO−), which is highly toxic for sperm as it rapidly reacts with its proteins, lipids, and DNA. The consequent membrane damage compromises various sperm functions, including motility.

In the present study, it was found that among the infertile males, a statistically significant reduction of parasympathetic activity and a statistically significant increase in sympathetic activity. This indicated men with poor semen quality group are exposed to a high level of stress. Therefore, it was found that there is a direct association between poor semen quality and cardiac autonomic dysfunction.

We propose that a male population with poor semen quality affect negatively cardiac autonomic modulation in the form of reduced HRV. Reduced HRV is likely to be an early indicator of cardiac autonomic dysfunction even at subclinical stages. Therefore, HRV is an especially useful tool to detect the stress and management of stress to maintain reproductive health. We further propose the need to develop a clear policy for early detection and management of cardiac autonomic dysfunction and improvement of the availability and affordability of stress management among infertile males to improve their reproductive health, to solve sterility problems and to enjoy the sexual life happily.
Limitation of the study: This study was done with short term HRV which may provide limited reflection of only cardiac autonomic stress. To get full reflection of autonomic stress, we suggest recording of 24-hour HRV with inclusion of other autonomic tests.

CONCLUSION:
There is a strong association between infertility and stress among infertile males. Tracking HRV may be a great gold standard tool to motivate awareness of infertility-related stress. Males with impaired HRV or autonomic dysfunction should undergo their semen analysis and vice versa. To maintain reproductive health, lifestyle modifications, regular physical exercise including yoga and psychological therapies in the management of stress-related infertility should be implemented. By understanding the impact of stress on semen quality, and by actively modifying lifestyle behaviours, men can control their own fertility potential and can enjoy a healthy reproductive life.

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