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ANALYSIS OF HEART RATE VARIABILITY AMONG FEMALES WITH IRON DEFICIENCY ANEMIA

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Abstract

Background: Iron deficiency anemia (IDA) is a widespread nutritional disorder affecting millions globally, particularly women and children. IDA has significant implications for cardiovascular health, including autonomic dysfunction, which can be assessed through heart rate variability (HRV) analysis. This study aims to evaluate autonomic function in females with IDA by comparing HRV parameters with those of healthy controls. **Materials and Methods:** A case-control study was conducted at Madras Medical College, Chennai, involving 80 female participants aged 18-45 years. The study group included 40 females with clinically diagnosed IDA, and the control group comprised 40 healthy females. HRV was measured using the Medicaid Physiopac 8-channel HRV recorder. Key HRV parameters, including Mean RR, Mean HR, SDNN, RMSSD, LF, HF, and LF/HF ratio, were analyzed and compared between the groups. Statistical analysis was performed using SPSS software, with p <0.05 considered statistically significant. **Result:** The study found that females with IDA had significantly higher mean heart rates (87.23±7.63) and lower Mean RR intervals (704.80±115.69) compared to controls. HRV analysis revealed a significant decrease in parasympathetic indicators, including SDNN (39.39±8.37) and RMSSD (33.43±6.12), and an increase in sympathetic indicators such as LF (56.49±11.63) and LF/HF ratio (1.57±0.94). These findings suggest increased sympathetic activity and reduced parasympathetic tone in IDA patients. The study also found significant differences in blood pressure, with lower systolic and diastolic values in the IDA group. **Conclusion:** The study concludes that IDA in females is associated with significant autonomic imbalance, characterized by reduced parasympathetic activity and increased sympathetic dominance. HRV analysis serves as a sensitive and non-invasive tool to detect early autonomic dysfunction in IDA, allowing timely intervention to prevent cardiovascular complications. Early diagnosis and treatment of IDA can help mitigate the risk of adverse cardiovascular outcomes associated with autonomic dysfunction.

INTRODUCTION

Iron deficiency anemia (IDA) is one of the most prevalent nutritional disorders globally, affecting both industrialized and non-industrialized nations. This condition particularly impacts children and women, with South Asia and India reporting high prevalence rates—up to 88% in pregnant women and 74% in non-pregnant women.[1] The prevalence of IDA varies significantly across age groups, sexes, and economic statuses, with estimates suggesting that nearly three-fourths of the global population may be iron deficient.[2] According to WHO, about 2 billion people suffer from IDA, with 8% affected in developed countries and 36% in developing countries (WHO 2007).

Iron deficiency not only affects overall health but also has implications for cardiovascular health, leading to increased risks of conditions like cardiomyopathy, chronic mitral regurgitation, congestive heart failure, and myocardial infarction, all of which are associated with decreased heart rate variability (HRV) and increased mortality.[3-6]

Iron deficiency occurs when iron stores are depleted, leading to insufficient iron supply to tissues, including red blood cells. This condition is most common in growing children, pregnant and lactating women, and adolescents. In IDA, hemosiderin and ferritin levels decrease, reducing the supply of iron to apotransferrin, lowering transferrin saturation, and increasing transferrin receptors. WHO defines IDA as hemoglobin less than 12 g/dL and serum ferritin less than 12 ng/mL.

NHANES III data indicate a higher prevalence of IDA among children and women, particularly adolescent girls and women of childbearing age (12-49 years). Risk factors include menstrual blood loss, inadequate dietary iron, and bioavailability issues. Ligand substances like ascorbic acid enhance non-heme iron absorption, while others like phytates and calcium inhibit it. High-risk groups include pregnant women, women of reproductive age, children under 5, adolescents, and the elderly.

IDA progresses in stages, starting with the depletion of storage iron (low serum ferritin), followed by decreased transport iron (latent iron deficiency), and finally, a significant reduction in hemoglobin synthesis, leading to microcytic, hypochromic anemia. Clinically, IDA manifests as pallor, fatigue, glossitis, koilonychia, and in children, irritability and pica. Untreated, IDA can lead to serious complications, including heart failure and death. HRV, an indicator of autonomic dysfunction, is a critical tool for predicting sudden cardiac arrest and arrhythmias in these patients.[7-10]

Heart rate variability (HRV) refers to the beat-to-beat variation in the duration of the cardiac cycle, specifically the RR intervals, measured in milliseconds (ms). This variation is present even in the resting state and reflects the intrinsic activity of the sinoatrial (SA) node, which is modulated by the autonomic nervous system. The RR interval is the time between two consecutive heartbeats and can be measured using echocardiography.

HRV is an important non-invasive method to assess the integrity and autonomic function of the heart by analyzing the beat-to-beat variations in heart rate. The autonomic nervous system's balance between sympathetic and parasympathetic influences on the heart is reflected in the variations of the RR interval.[11]

The intrinsic firing rate of an uninnervated human SA node is about 100 beats per minute. When innervated, sympathetic stimulation increases the heart rate, while parasympathetic stimulation via the vagus nerve decreases it. Typically, vagal tone predominates over sympathetic tone, keeping the resting heart rate below 100 beats per minute.[12]

Research has demonstrated that the sympathetic and parasympathetic innervation of the SA node contributes to heart rate variability. HRV is constantly influenced by external and internal stimuli and is regulated by the autonomic nervous system. It can be assessed using cardiac autonomic function tests, which evaluate both parasympathetic and sympathetic responses through the analysis of HRV. These tests, as recommended by the Task Force, include the Resting HRV, which is a sensitive, specific, and easy-to-perform non-invasive tool.[13]

Increased HRV indicates a heart's ability to adapt flexibly to various influences, suggesting a balanced autonomic function. Conversely, decreased HRV reflects impaired autonomic function and reduced adaptive capacity.

In this study, HRV analysis is utilized to diagnose the autonomic imbalance between the sympathetic and parasympathetic systems in women with iron deficiency anemia. We aim to use both Time domain and Frequency domain methods of Resting HRV to determine sympathovagal balance.

Aim & Objective

To compare the heart rate variability among female patients with iron deficiency anemia and normal female population.

MATERIALS AND METHODS

This case control study was conducted at the Institute of Physiology & Experimental Medicine, Department of Hematology, and Institute of Internal Medicine, Madras Medical College, Chennai, from April 2017 to March 2018. The study population included females aged 18-45 years, with and without iron deficiency anemia, visiting RGGGH, Chennai. Inclusion criteria for the anemic group were hemoglobin levels <12 gm% and Complete Blood Count parameters (MCV, MCH, MCHC, RDW) showing values lower than the normal range, with a peripheral smear indicating microcytic hypochromic anemia. Exclusion criteria included other forms of anemia, structural heart diseases, diabetes, hypertension, renal failure, thyroid disorders, pregnancy, chronic infections or inflammations, radiation exposure, drug intake, autoimmune disorders, and malignancy. The sample size was calculated based on the previous study results using Openepi software and found to be 80. About 40 in each group. The institutional human ethics committee approval was obtained.

One group is those with iron deficiency anemia and another group is normal female population without iron deficiency anemia. After explaining the study and getting informed consent from them, the study was conducted. Data was collected using a semi structured questionnaire. Investigations were done for patients which includes complete blood count, heart rate variability.

Under universal sterile precautions, 5 ml of venous blood was collected for complete blood count (CBC), and peripheral smear (PS) analysis. Heart rate variability (HRV) of the selected subjects was recorded using the Medicaid Physiopac 8-channel HRV recorder, equipped with in-built software for data analysis. After explaining the procedure and obtaining consent, participants were instructed to ensure good sleep, have breakfast 2 hours prior, avoid caffeine, nicotine, and alcohol, wear loose clothing, remove accessories, and relax. The recording was conducted between 10 am and 12 noon in a quiet, temperature-controlled room. Participants rested in a supine position for 10-15 minutes before electrode placement. Limb leads were attached after cleaning the areas with spirit, and the ECG was recorded for 5

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minutes using lead II. The data was analyzed using short-term HRV analysis software, with artifact screening, and key parameters like Mean RR, Mean HR, SDNN, RMSSD, Low Frequency, High Frequency, and LF/HF ratio were estimated through power spectral analysis using Fast Fourier Transformation.

Data was entered in MS Excel and analysed using SPSS software version 21. Continuous variables are expressed in mean, standard deviation, Categorical variables are expressed in numbers and percentages. Inferential statistics like were used and p <0.05 was considered statistically significant.

RESULTS

In our study, 40 patients who were clinically diagnosed of Iron deficiency anemia were tested for assessment of their autonomic functions by using the Heart rate variability analysis and the estimated values are compared with that of 40 clinically healthy individuals.

The mean age of the study group was 32.1±7.7, where the control group were of mean age of 29.18±7.32 and the female Patients with Iron deficiency anemia were of mean age of 35.1 ±6.98. The mean value of weight for the control group and the female patients with Iron deficiency anemia were 49.7 ±11.1 and 164.12 ±11.7 respectively. The mean value of BMI for the control group and the female patients with Iron deficiency anemia were 21.4 ±2.5 and 22.3 ±1.9 respectively. The mean value of Hemoglobin for the control group and the female patients with Iron deficiency anemia were 12.76 ±0.64 and 9.46 ±1.49 respectively. [Table 1]

The blood pressure parameters, systolic and diastolic blood pressure as well as the heart rate at the resting levels were compared between the control group and female patients with Iron deficiency anemia. A very highly significant increase in mean heart rate (85.38±5.8, p<0.001) is observed in female patients with iron deficiency anemia when compared to that of the control group(78.28±5.26). This could be mainly due to sympathetic overactivity in patients with Iron deficiency anaemia. The resting systolic blood pressure in female patients with Iron deficiency anemia showed a significantly lower value (103.55±9.47, p<0.001) compared to that of the control group (112.95±9.40). The decrease in systolic blood pressure could be due to anemia. The resting diastolic blood pressure in female patients with Iron deficiency anemia showed a significantly lower value (69.60±6.87, p<0.014) compared to that of the control group (73.10±5.43). Diastolic blood pressure reflects the peripheral resistance, here in this study the decrease in DBP indicates the decrease in afterload due to adaptability changes that occur in anemia. [Table 2]

Table 1: Comparison of socio-demographic details between the control group and patients with Iron deficiency anemia.

Variables	Control group, n=40		IDA patients, n=40	
	Mean	**SD**	**Mean**	**SD**
Age (years)	29.18	7.32	35.1	6.98
Height (cm)	161.32	12.5	*164.12	11.7
Weight (Kg)	49.7	11.1	*51.4	9.8
BMI	21.4	2.5	*22.3	1.9
Hemoglobin (gm/dl)	12.76	0.64	*9.46	1.49

*p value<0.05 is considered as statistically significant. IDA = patients with Iron Deficiency Anemia. BMI= Body Mass Index.

Table 2: Comparison of the Resting heart rate, resting systolic blood pressure and resting diastolic blood pressure between the control group and female patients with iron deficiency anemia

Variables	Control group, n=40		IDA patients, n=40	
	Mean	**SD**	**Mean**	**SD**
Resting Heart rate (beats/min)	78.28	5.26	***85.38	5.83
Resting SBP(mm/Hg)	112.95	9.4	***103.55	9.47
Resting DBP (mm/Hg)	73.1	5.43	*69.6	6.87

*p<0.05 which is considered statistically significant. ** p value < 0.01 was considered as highly significant. SBP=systolic blood pressure, DBP=diastolic blood pressure.

Table 3: Comparison of the heart rate variability factors between the control group and female patients with iron deficiency anemia

Variable	Study group	N	Mean	SD
Mean Heart Rate (beats/min)	Control	40	77.20	6.19
	IDA	40	***87.23	7.63
Mean RR interval (ms)	Control	40	804.68	84.46
	IDA	40	** *704.80	115.69
Mean SDNN (ms)	Control	40	44.14	8.14
	IDA	40	**39.39	8.37
Mean RMSSD (ms)	Control	40	39.22	6.37
	IDA	40	***33.43	6.12
Mean LF(nu)	Control	40	44.8	8.28
	IDA	40	***56.49	11.63
Mean HF(nu)	Control	40	54.92	7.97
	IDA	40	* * * 42.46	12.53

Mean LF/HF ratio	Control	40	0.86	0.33
	IDA	40	** *1.57	0.94

*p<0.05 which is considered statistically significant. **p value < 0.01 was considered as highly significant. IDA = patients with Iron Deficiency anemia.

The mean Heart rate in female patients with Iron deficiency anemia was found to be significantly increased (87.23±7.63, p<0.001) when compared to that of the controls (77.20±6.19). Increased mean heart rate of HRV analysis in Iron deficiency anemia indicates the possibility of sympathetic overactivity. The mean RR interval in female patients with Iron deficiency anemia was found to be significantly decreased (704.80±115.69, p<0.001) when compared to that of the controls (804.68±84.46). Mean RR interval (ms) of HRV analysis reflects inter beat intervals. Decreased mean RR interval in Iron deficiency anemia indicates the possibility of reduced vagal tone. The mean SDNN in female patients with Iron deficiency anemia was found to be significantly decreased (39.39±8.37, p<0.012) when compared to that of the controls (44.14±8.14). Mean SDNN of HRV analysis reflects parasympathetic function. Decreased mean SDNN in patients with Iron deficiency anemia indicates the possibility of reduced parasympathetic activity. The mean RMSSD in female patients with Iron deficiency anemia was found to be significantly decreased (33.43±6.12, p<0.001) when compared to that of the controls (39.22±6.37). Mean RMSSD of HRV analysis reflects parasympathetic function. Decreased mean RMSSD in patients with Iron deficiency anemia indicates the possibility of reduced parasympathetic tone. The mean LF in female patients with Iron deficiency anemia was found to be significantly increased (56.49±11.63, p<0.001) when compared to that of the controls (44.8±8.28). Mean LF of HRV analysis reflects sympathetic function. Increased mean LF in patients with Iron deficiency anemia indicates the possibility of sympathetic over activity. The mean HF in female patients with Iron deficiency anemia was found to be significantly decreased (42.46±12.53, p<0.001) when compared to that of the controls (54.92±7.97). Mean HF of HRV analysis reflects parasympathetic function. Decreased mean HF in patients with Iron deficiency anemia indicates the possibility of reduced parasympathetic tone. The mean LF/HF ratio in female patients with Iron deficiency anemia was found to be significantly increased (1.57 ±0.94, p<0.001) when compared to that of the controls (0.86 ±0.33). Mean LF/HF ratio of HRV analysis reflects sympathovagal balance. Increased mean LF/HF ratio in patients with Iron deficiency anemia indicates sympathetic overactivity. [Table 3]

DISCUSSION

Iron deficiency anemia has been found to be associated with increased cardiovascular morbidity and mortality. It affects cardiac function. Decreased Heart rate variability (HRV) has been found to be associated with increased mortality and morbidity in several heart disorders like myocardial infarction, cardiomyopathy, congestive heart failure and chronic mitral regurgitation.[14-17]

The physiological change which occurs in anemia is a compensatory increase in cardiac output, preload, heart rate, stroke volume associated with a decrease in the afterload. This increase in sympathetic activity causes palpitation, tachycardia in iron deficiency anemic patients18 and Progression of iron deficiency anemia results in cardiomyopathy.

Mechanism behind this pathogenesis has not been fully understood so far. But there are many advancing research trails related to this that have led to the formation of new hypothesis. This study was primarily aimed to analyze the cardiac autonomic function in Iron deficiency anemia by doing Heart rate variability analysis. Forty iron deficiency female subjects and forty age and gender matched normal controls were included in our study. The study group were selected between the age group of 18 to 45 years females.

The mean age of the control group was 35.10 ± 6.98 and the mean age of female patients with Iron deficiency anemia was 29.18 ± 7.32. The difference was not significant in relation to age. This was in consistent with the earlier studies. The mean height of the control group was 161.32±12.5 and the mean height of female patients with Iron deficiency anemia was 164.12 ±11.7.The mean weight of the control group was 49.7±11.1 and mean weight of female patients with Iron deficiency anemia was 51.4±9.8.The mean BMI of the control group was 21.4±2.5 and the mean BMI of female patients with Iron deficiency anemia was 22.3±1.9. The difference was found to be significant in relation to height, weight and BMI.

The mean resting heart rate of control group was 78.28 ± 5.26 and the mean resting heart rate of female patients with Iron deficiency anemia was 85.38±5.83. An elevated level of sympathetic activity and decreased parasympathetic tone was seen in iron deficiency anemia patients as per results of the study done by Tuncer et al.[19] Our study showed there was increase in the mean heart rate in female patients with Iron deficiency anemia. The Possible reason for this could be the increase in the sympathetic activity of the iron deficiency anemia patients.

The mean resting systolic blood pressure in control group was 112.95± 9.40 and the mean resting systolic blood pressure in female patients with iron deficiency anemia was 103.55±9.47. Our study showed decreased systolic blood pressure in iron deficiency anemia female patients when compared to controls. Anemia leads to many adverse effects, and this is observed in many pathological conditions like end stage renal failure and myocardial infarction. But how presence of anemia progresses to heart failure is being evaluated recently only.[20-22] Studies show anemia patients with systolic dysfunction when not treated can progress to heart failure.[20,21,23-26]

The mean resting diastolic blood pressure in control group was 73.10±5.43 and the mean resting diastolic blood pressure in female patients with Iron deficiency anemia was 69.60±6.87. Our study showed decreased diastolic blood pressure in cases when compared to controls. This was consistent with the findings observed in the study done by Deepu Nair et al.[27]

There are many explanations regarding mechanisms concerned with relationship between anemia and diastolic dysfunction. Presence of anemia for prolonged period results in adaptation and this causes increase in heart rate, cardiac index, stroke volume and plasma volume.[28,29] All these changes of increased sympathetic activity and ionotropic activity leads to additional stress on myocardium.[30]

The mean hemoglobin in control group was 12.76 ±0.64 and the mean hemoglobin in female patients with Iron deficiency anemia was 9.46±1.49. Our study showed that there was decreased hemoglobin in female patients with Iron deficiency anemia when compared to controls. The hormonal, metabolic changes due to anemia also cause direct myocardial damage and also through salt, water retention indirectly exerts strain on the myocardium. This forms the basis of the hypothesis that anemic adaptability causes ventricular remodeling, diastolic dysfunction and systolic dysfunction.

Heart Rate Variability (HRV) analysis is considered as one of the effective, non- invasive tools to assess the function of the Autonomic nervous system. There occurs an increased risk of adverse cardiac events when there is alteration in resting HRV. Analysis of the resting heart rate variability by doing 5 minutes ECG recording using the HRV analysis among the study groups showed the following results.

Mean HR, Mean RR, SDNN, RMSSD were the variables taken for analysis in our study as prescribed by the Task force. Our findings showed decreased HRV in female patients with Iron deficiency anemia. Decreased HRV suggests either increased sympathetic tone or decreased parasympathetic tone. The Mean HR was significantly increased in female patients with Iron deficiency anemia (87.23±7.63) when compared to controls (77.20±6.19). This shows tachycardia in the Iron deficiency anemia patients. This finding was consistent with the findings observed in the studies done by Tuncer et al.[19] The Mean RR among the study groups were measured which shows decreased mean RR interval (704.80±115.69) in the female patients with Iron deficiency anemia when compared with controls (804.68±84.46). Similar findings were also observed in studies done by Yokusoglu et al.[31]

In our study female patients with Iron deficiency anemia showed decreased mean values of SDNN (39.39±8.14) and RMSSD (33.43±6.12) when compared with the normal controls SDNN (44.14±8.14) and RMSSD (39.22±6.37). This was also consistent with the findings of Farhana rahman et al.32 Similar finding was also observed in studies done by Yokusoglu et al.[31]

Results from studies done by Shetty KP et al,[33] and Tuncer et al,[19] showed there is no difference in the HRV parameters in iron deficiency anemia patients and normal subjects except mean HR. Lufti et al,[34] reported no significant difference in values of SDNN and RMSSD in Iron deficiency anemia and healthy controls.

But our study results show decreased SDNN and RMSSD which indicates that parasympathetic activity is decreased in iron deficiency anemia when compared with normal subjects. The SDNN, RMSSD were considered as sensitive indicators of parasympathetic function and thereby a significant low value indicates reduced vagal activity in Iron deficiency anemia patients.

LF, HF and LF/HF ratio were the variables taken for analysis in our study as prescribed by the Task force. A significant variation was observed in the frequency domain variables among the study groups. The LF values in normalized units(nu) which is an indicator of sympathetic tone was significantly higher in female patients with Iron deficiency anemia (56.49±11.63) when compared with normal controls. (44.81±8.28). The HF values in normalized units(nu) which is an indicator of parasympathetic tone was found to be significantly lower in female patients with Iron deficiency anemia (42.46±12.53) when compared with the control (54.92±7.97). As the HF power indicates the vagal activity, our study finding suggest that there is decreased parasympathetic activity in female patients with Iron deficiency anemia. Our study findings were consistent with findings of Lufti et al.34 His study showed VLF, LF, HF, TP was positively correlated with hemoglobin concentration. HRV parameters were found to be decreased. Study by Gehlot Pinkesh et al shows that there was no statistically significant relation between hemoglobin and HRV in anemia.[35]

LF/HF ratio was increased in iron deficiency individuals (1.57±0.94) when compared with the controls (0.86±0.33) due to sympathovagal imbalance. This ratio signifies the overall balance between sympathetic and parasympathetic system. In addition, sympathetic stimulation enhances erythropoiesis. Studies of Biaggioni et al supports this hypothesis. Sympathetic stimulation in anemia stimulates erythropoiesis. These cases with autonomic dysfunction showed good response to erythropoietin therapy.[36]

Therefore, in our study it was found that parasympathetic activity decreases and sympathetic activity increases in patients with iron deficiency anemia.

The possible reason is, in iron deficiency anemia due to decreased hemoglobin concentration the oxygen carrying capacity of blood is decreased which leads to hypoxia. This hypoxia will be sensed through the carotid bodies which influences the cardiovascular centers leading to increase in the sympathetic activity.[37] The mechanism causing carotid body activation is supposed to be either due to hypoxia related mitochondrial respiratory chain inhibition or due to potassium channel suppression that causes intracellular calcium accumulation.[38]

This type of anemic hypoxia stimulates the adrenergic nervous system. Stimulation of this leads to the cardiovascular response like tachycardia and increased cardiac output. These changes will try to compensate the decrease in the oxygen content of the blood. Moreover, the activation of the adrenergic system can be known by estimating the concentration of plasma and urine epinephrine,[39] which is not done in our study.

These patients have low basal parasympathetic outflow and as a compensatory mechanism there is an increase in the heart rate. So these changes in HRV has been taken as a sensitive indicator of health deterioration due to autonomic changes.[40]

Hence HRV is used as early and better qualitative and quantitative method to detect the autonomic impairment. High HRV indicates well-functioning of the autonomic nervous system and on the other hand when HRV is reduced it acts as a risk indicator to know the adverse complications in the patients suffering from wide range of diseases.[41] So, in our study HRV has been used to know the cardiovascular mortality in female patients with Iron deficiency anemia. There are studies which have reported that supplementation of iron can improve the dysregulated autonomic nervous system reflexes.[42]

So our study has been aimed to diagnose Heart rate variability by HRV analysis as early as possible to avoid the morbidity and mortality due to cardiovascular changes by assessing the autonomic imbalance, So that by supplementing iron therapy it is possible to prevent the cardiovascular complications in these patients.

CONCLUSION

The sympathetic and parasympathetic activity and the functional status of the heart were evaluated in iron deficiency anemia female patients using Resting Heart rate variability. This study concludes that there is an autonomic imbalance as evidenced by decrease in SDNN, RMSSD which were indicators of parasympathetic and increase in LF power (nu) showing the sympathetic activity. The ratio between LF and HF was increased in iron deficiency anemia individuals which showed sympathetic dominance of autonomic nervous system activity. So, by using HRV analysis as a sensitive and non-invasive tool, treatment can be started at the earliest and thus we can prevent the complications in iron deficiency anemia.

Limitations

Our study has involved a smaller sample size. It is necessary to apply it to a general population using larger sample size to get better outcome of the study.

The duration of the disease and autonomic dysfunction was not correlated in our study.

The study has evaluated only the resting autonomic activity and not the response of the autonomic nervous system to various external stimuli or lab stressors, which is a drawback for the study.

One of the mechanisms suggested for autonomic dysfunction is elevated circulating nor epinephrine levels and urine norepinephrine concentration. Hence our study needs to be substantiated by measurements of the catecholamine, norepinephrine levels which is not done in our study.

Moreover, blood gas analysis was not done for anemic hypoxia.

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