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RESEARCH ARTICLE

ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTION IN SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT

Objective: Studies investigating systolic and diastolic left ventricle function in subclinical hypothyroidism (ScH) have shown controversial results. As myocardium is a target organ of thyroid hormone action, the aim of the study was to assess the left ventricular systolic and diastolic function in ScH.

Methods: Fifty-four patients with newly diagnosed ScH and 30 euthyroid controls, patients of the University Clinic of the Endocrinology, Diabetes, and Metabolic Disorders Clinic were enrolled. Transthoracic echocardiography, using M-mode, two-dimensional (2D), pulsed, continuous and color-Doppler, and advanced echocardiographic modalities Tissue Doppler and two-dimensional speckle tracking was performed in all subjects.

Results: Although normal echocardiographic values of all measured parameters, SCH patients were significantly different from their matched controls: the ratio between E/A was statistically significantly lower (1,26±0,36 vs. 1,03±0,29, p<0,01), the ratio between E/e' sep. was statistically significantly higher (6,04±1,64 vs. 7,62±2,29, p<0,01), MPI was statistically significantly higher (0,43±0,07 vs. 0,47±0,08, p<0,05), GLS had statistically significantly lower negative value (-20,9±1,7 vs. -19,55±2,3%, p<0,001), and S/TDI was statistically significantly lower (0,092±0,011 vs. 0,077±0,013, p<0,01). TSH negatively correlated with EF (r=-0,15, p<0,05), E/A(r=-0,14, p<0,05), GLS (r=-0,26, p<0,001), S/TDI (r=-0,22, p<0,01), and positively correlated with E/e 'sep. (r=0,14, p<0,05).

Conclusion: Subclinical hypothyroidism contributes to changes in certain parameters involved in the assessment of global and longitudinal systolic and diastolic left ventricular function compared to healthy individuals.

INTRODUCTION

Subclinical hypothyroidism (ScH) is a condition defined as normal serum levels of thyroid hormones and elevated thyroid stimulating hormone (TSH) levels. It is often asymptomatic, diagnosed by laboratory findings. The prevalence is higher in women and with increasing of the age (Sawin *et al,* 1979). Two-thirds of patients with ScH have mild subclinical hypothyroidism, (TSH values below 10,0mU/L), where the decision for treatment is unknown (Pearce *et al*, 2013). Heart and vessels are sensitive to minimal changes in thyroid hormone levels (Klein and Ojamaa, 1992). Non-invasive techniques have been used to assess cardiac function in ScH. Several studies compared left ventricular echocardiography parameters between patients with ScH and a control group showing contradictory results. (Biondi *et al*, 1999) showed no differences, but (Monzani *et al*, 2001) showed left ventricular diastolic dysfunction in patients with ScH. (Vitale *et al*, 2002) using Tissue Doppler Imaging (TDI) showed diastolic dysfunction in patients with ScH. Analyzing the literature it can be seen that most of the studies analyzed a small group of patients with predominantly higher values of TSH. This study was designed to identify possible impairment of left Ventricular systolic and diastolic function in ScH, including mostly patients with lower values of TSH.

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MATERIAL AND METHODS

Patients

The prospective study was conducted at the University Clinic of Endocrinology, and the University Clinic of Cardiology in Skopje, R. Macedonia. The study included the observation of two patient groups: control and ScH group. During the period of three years, 54 consecutive patients with newly diagnosed ScH and 30 healthy euthyroid patients were analyzed. The criteria for the diagnosis of ScH were: TSH> 4.2mU / L with normal serum FT4 10.3-24.45 pmol/L and FT3 4.2-8.1 pmol/L. Euthyroid persons in the control group had normal FT4, FT3, and TSH (0.2-4.2 mU/L). Only 5 patients with ScH have TSH value above 10.0mU/L.

Exclusion criteria

Patients with previous history of thyroid disease, receiving therapy for thyroid or cardiovascular function were not included. Patients with cardiovascular disease, hypertension, cigarette smokers, hypothalamic-pituitary disease, depression, psychosis, bipolar disorders, diabetes, chronic pancreatitis, hepatic, renal disease, ovulatory dysfunction, infertility, and pregnancy were also not included.

Ethical aspects

All patients gave informed consent to participate in the study after careful explanation of the testing protocol. The study was made in accordance with the Declaration of Helsinki and approved by the Ethics Committee at the Medical Faculty in Skopje.

METHODS

At the first visit to the University Clinic of Endocrinology Clinic, blood for TSH, FT4, and FT3was taken. At the Outpatient Department of Cardiology Clinic trans thoracic echocardiography was done. Using M-mode, 2D, Doppler and Pulse Wave Tissue Doppler Imaging (PW TDI) echocardiography of the left ventricular systolic and diastolic function were assessed.

Laboratory tests

All blood samples for thyroid hormones were collected from the antecubital vein in the morning. TSH, FT4 and FT3 were determined by the super-sensitive chemiluminescent immuneassay (Immulite 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). The functional sensitivity for TSH was 0.004 μIU / mL, for FT4, 0.3ng / dL and FT3 0.4ng / dL.

Echocardiographic measurements

Echocardiographic examination was performed with the Subjects in partial left decubitus using a Vivid 7 ultrasound machine of General electronics at the University Clinic of Cardiology, in Skopje. The analyses of the parameters were made with off-line analysis of the memory image at the work station. To obtain certain parameters all echocardiographic modalities were used: M-mode, two-dimensional (2D) echocardiography, pulsed, continuous and color-Doppler, and advanced echocardiographic modalities Tissue Doppler and two-dimensional speckle tracking. Conventional long and short axis, apical 2, 3, and 4-chamber views were used, according to the recommendations of the American Society of Echocardiography (ASE) (Lang *et al,* 2015). With M-mode quantitative analysis according to the recommendations of ASE in parasternal long axis view we analyzed the following parameters: end-diastolic diameters (LVEDD), the left ventricular posterior wall (PW), interventricular septum thickness (IVS), left atrial diastolic diameter (LA).

The assessment of global LV systolic function was determined by using the "Biplane" disc method (the modified rule of "Simpson"). This method is also recommended by the ASE (Sunbul *et al,* 2013). Ventricular volumes were calculated in two apical windows (apical 4-chamber and apical 2-chamber view) at end-diastole and end-systole. Then, using computer software, the following parameters were determined: left ventricular end-systolic (LVESV) and end-diastolic (LVEDV) volumes, ejection fraction (EF), and the area of the left atrium (LA area). The left atrial volume index (LAVI) was calculated as LA area corrected by body surface area, measured by Mosteller (Lang *et al,* 2005).

Transmitral Doppler inflow and tissue-pulsed Doppler (TDI) were obtained in the apical 4-chamber view. The following parameters were measured: transmitral early diastolic peak flow velocity (E), late diastolic flow velocity (A), their ratio (E/A), the duration of the atrial contraction (A dur), and E velocity deceleration time (DT). A sample volume of 5 mm was placed from the site of the septal and lateral insertion of the mitral cusps, using TDI in 4-chamber view. In order to minimize artifacts minimal intensity (gain) Doppler and low wall filter were used. Thus the angle between the ultrasound wave and the analyzed myocardial segment was not greater than 30°.

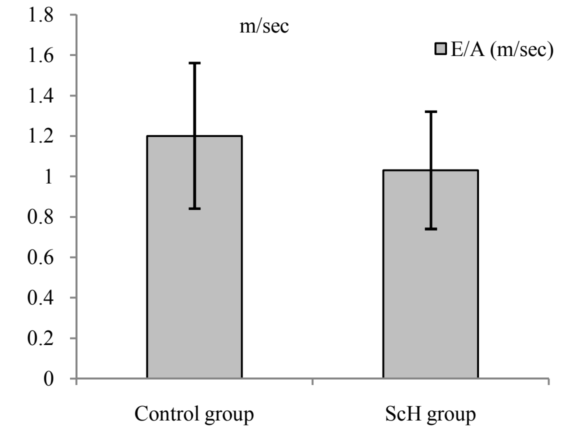
The maximum systolic velocity (S), peak early diastolic velocity (e’), and peak atrial diastolic velocity (a') were measured. Using E and e’ parameters, the following derivate parameters which showed LV diastolic function were calculated: ratio E/e’ lat., where e’ lat. was the speed of the early diastolic myocardial relaxation measured lateral, E/e’ sep., where e’ sep. was the speed of the early diastolic relaxation measured septal, E/e’ average, where e’ average was the average value of E/e 'lat. and E/e' sep. Using TDI in the same apical 4-chamber view, the isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT), and ejection time (ET) were measured. All measurement was determined as the average of measurements in three consecutive heart cycles. Myocardial performance index (MPI) was calculated by the formula MPI= IVCT + IVRT / ET, derived by TDI. Myocardial perfusion index is a parameter that provides information about global, systolic and diastolic function.

The flow through the pulmonary veins (PV) showing diastolic function was determined in the apical 4-chamber view using pulse wave Doppler. The following parameters were measured: systolic velocity through the pulmonary veins (s), diastolic velocity through the pulmonary veins (d), their ratio (s/d), and retrograde pulmonary venous flow during the atrial contraction-atrial reversal (Ar).

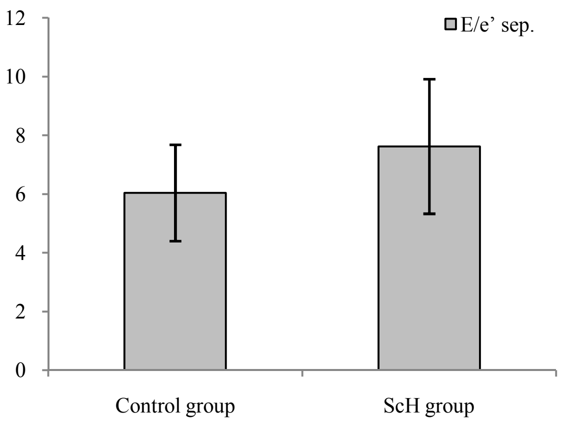
Speckle tracking two dimensional echocardiographic technique for assessment of global deformation of LV and assessment of global longitudinal systolic function was performed. Three apical sections 2, 3, and 4-chamber views were used, labeling endocardium and automatic assessment global deformation of LV was obtained. The global strain gives us information about the global longitudinal LV systolic function.

Statistical Analysis

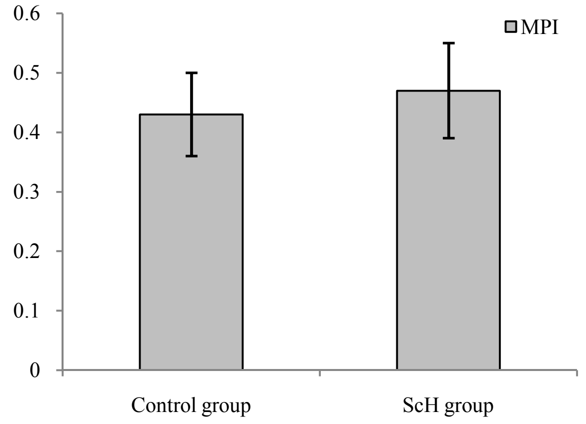
Data was analyzed using Statistics Package 7.0 for Windows program. The results are presented as the average ± standard deviation or percentages. The normal distribution of variables was verified with the Shapiro-Wilk test. As the distribution was normal, Student's independent t-test was used for the comparison of quantitative data between the two groups. For the comparison of categorical variables the chi-square test, Yates correction was used. The correlation between the tested parameters was determined using Pearson correlation. $p < 0.05$ was taken a statistically significant.



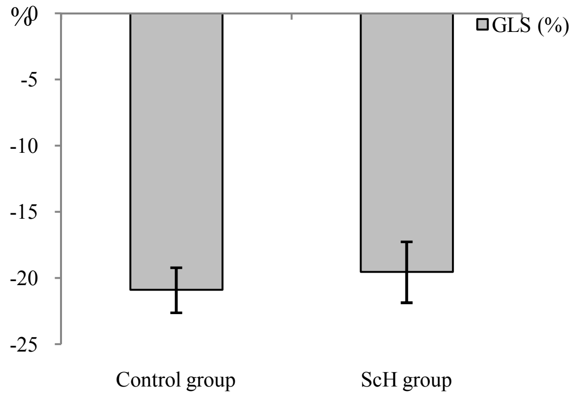
Graph 1 Average values of E/A in the both analyzed groups



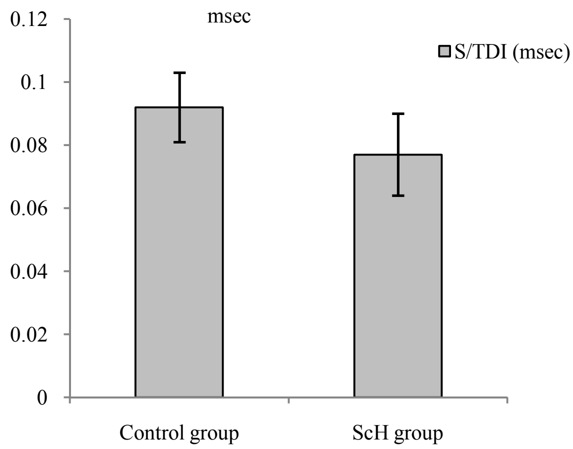
Graph 2 Average values of E/e' sep. in the both analyzed groups



Graph 3 Average values of MPI in the both analyzed groups



Graph 4 Average values of GLS in the both analyzed groups



Graph 5 Average values of S/TDI in the both analyzed groups

RESULTS

The differences in echocardiographic parameters between the control and ScH group are presented in Table 1. In both groups there was no difference in age, sex, body mass index, and body surface area. As expected, the mean serum TSH level in the ScH group was significantly higher when compared to the control group (Table 1). The mean TSH value was 8.1±2.3mU/L, which shows that most of the patients with ScH have mild ScH. Only 5 patients or 9.2% of the patients from ScH group have TSH values above 10.0mU/L. Also, the values of FT4 and FT3 were significantly lower in ScH group.

Table 1 Demographic, hormonal and echocardiographic parameters

	Control group n=30	ScH group n=54	Statistical significance
sex	3 : 27 (10%)	2:52 (3,7%)	NS*
Age (years)	39,3 ± 11,7	43,1±12,4	NS
BMI (kg/m2)	24,3 ± 3,0	26,7 ±4,2	NS
BSA (m^2)	1,78±0,15	1,79±0,17	NS
TSH mU/L	1,7 ± 1,05	8,1 ± 2,3	p<0,001
fT4 pmol/L	15,4 ± 2,2	12,3 ± 2,0	p<0,01
fT3 pmol/L	5,2±2,1	4,5±1,1	p<0,05
LA area (cm^2)	13,7±1,8	13,1±2,7	NS
LA (mm)	31,7±3,1	31,3±3,9	NS
LAVI (ml/m^2)	24,43±4,31	21,95±5,77	NS
LVEDd (mm)	46,0±4,8	46,4±4,3	NS
LVED vol (ml^3)	79,1±11,9	81,7±18,4	NS
LVES vol (ml^3)	31,3±7,0	31,6±7,8	NS
EF (%)	62,8±2,3	61,6±4,4	NS
FS (%)	33,9±2,5	33,6±3,2	NS
IVS (mm)	10,4±1,1	10,8±0,9	NS
PW (mm)	8,7±1,2	8,7±1,2	NS
E/A (m/sec)	1,26±0,36	1,03±0,29	p<0,01
DT(msec)	156,8±29,7	167,94±38,6	NS
E/e' sep.	6,04±1,64	7,62±2,29	p<0,01
E/e' lat.	6,08±1,24	6,35±1,62	NS
E/e' average	6,06±1,24	6,98±1,9	NS
A dur (msec)	117,9±16,8	112,18±17,2	NS
Ar dur (msec)	98,64±14,4	86,94±15,9	p<0,01
IVCT (msec)	60,04±10,9	64,14±13,4	NS
IVRT (msec)	66,39±8,3	67,27±13,7	NS
MPI	0,43±0,07	0,47±0,08	p<0,05
s/d	1,26±0,11	1,26±0,16	NS
pericarditis	6/30 (20%)	15/54 (27,8%)	NS*
GLS (%)	-20,9±1,7	-19,55±2,3	p<0,001
S/TDI (msec)	0,092±0,011	0,077±0,013	p<0,01
Ar-A	-18,87±10,78	-25,2±16,1	p=0,08

Showed results are average± standard deviation and percentes. NS- no significance.* chi-square test, Yates corection.

All echocardiographic measurements were in normal range, but there were statistically significant differences between some echocardiographic parameters in the two groups. Left ventricular measurements and volumes were normal between the two groups (Table 1). The ratio between E/A was statistically significantly lower (Graph 1), the ratio between E/e' sep. was statistically significantly higher (Graph 2), MPI was statistically significantly higher (Graph 3), GLS have statistically significantly lower negative value (Graph 4), and S/TDI was statistically significantly lower (Graph 5) in ScH group.

Average values for all analyzed parameters were in reference values, but lowering the ratio between E/A, increasing the ratio between E/e`sep., and prolongation in atrial contraction revealed to left ventricular diastolic dysfunction. Differences in S/TDI, MPI, and GLS represent the alteration in left ventricular systolic function (global and longitudinal) in ScH.

The correlation showed statistically significant negative correlation between TSH and EF (r=-0.15, p<0.05), negative correlation between TSH and ratio between E/A (r=-0.14, p<0.05), positive correlation between TSH and ratio between E/e'sep. (r=0.14, p<0.05), negative correlation between TSH and GLS (r=-0.26, p<0.001), and negative correlation between TSH and S/TDI (r=-0.22, p<0.01). With increasing of the TSH value, the left ventricular systolic (global and longitudinal) function decreased. Also, from lowering the ratio between E/A and increasing the ratio between E/e`sep., there is incipient diastolic dysfunction. FT4 positively correlated with E/A (r=0.18, p<0.05), negatively correlated with E/e'sep. (r=-0.17, p<0.05), negatively with MPI (r=-0.19, p<0.05), and positively with GLS (r=-0.18, p<0.05).

DISCUSSION

The study revealed the effect of ScH on left ventricular systolic and diastolic function. The ratio between E/A was statistically significantly lower and the ratio between E/e' sep. was statistically significantly higher. The ratio between E/A is a sensitive parameter for diastolic function. Thus, this result shows a mild diastolic dysfunction. A meta-analysis (Karabag *et al,* 2013) analyzed patients with ScH with an average age of patients similar to their age in this study, shows a statistically significant difference for the ratio E/A (1.0 ± 0.30 vs. 1.3 ± 0.36) as in our study. The average values for this parameter are similar to the average values in our research. The effect of ScH on the ratio E/A is confirmed by the statistically significant negative correlation between TSH and E/A, and the positive correlation between fT4 and E/A. The higher the TSH, fT4 proportionally declines, thereby decreasing the ratio E/A, i.e. diastolic dysfunction of the left ventricle occurs. Several studies (Karabag *et al,* 2013; Ozturk *et al,* 2012; Tadic *et al,* 2014) show diastolic dysfunction in ScH through extended DT and IVRT. In this study these parameters had a longer duration in the group with ScH, but without statistical significance.

The difference in the ratio E/e ' lat. was not large enough to be statistically significant. It is known that the parameter E/e` sep. is more sensitive in terms of the parameter E / e ' lat. when evaluating diastolic function of the left ventricle. In the study by (Ilic *et al*, 2013) which analyzed only the ratio E/e 'aver. There was a statistically significant difference between the control and the examined group. In the study made by (Karabag *et al*, 2013) the ratios E/e'sep. And E/e 'lat. were statistically significantly higher in the group with ScH vs. the control group. The same results were obtained by (Oner *et al*, 2011). This study proved the statistically significant positive correlation of TSH with E/e' sep., and the negative correlation of fT4 with E/e' sep. This means that with the increase of TSH or the decrease of fT4 E/e' sep. increases. The values of the ratios E/e' sep., E/e' lat. and E/e 'aver. were less than 8, which means normal left ventricular filling pressures. These normal left ventricular filling pressures talk only about initial changes in the diastolic function of the left ventricle, which in the analyzed groups was still in the normal range and could not be graded.

The parameter S/TDI which assesses the systolic function of the left ventricle was statistically significantly lower in the examined group compared to the control group. This proves the impaired longitudinal systolic function of the left ventricle in ScH, which is the first affected during the impairment of the left ventricular systolic function (Yu *et al,* 2007; Ho and Solomon, 2006; Gillam and Otto, 2012). In the study by (Ilic *et al,* 2013) this parameter in ScH was also statistically significantly lower. In this study, as in the study made by (Ozturk *et al*, 2012), TSH negatively correlated with S/TDI. These results confirm the connection of ScH with the systolic \

function of the left ventricle.

In this study MPI was statistically significantly higher in the examined group versus the control group (0.47 ± 0.08 vs. 0.43 ± 0.07). This parameter shows the global, or both the systolic and the diastolic function of the left ventricle. Identical results were obtained by (Oner *et al*, 2011). It is a case-control study which compared 27 patients with ScH, as opposed to 22 as the control group. In the case-control study by (Ilic *et al*, 2013) there is also a statistically significant difference between the control and examined group. The study by (Erkan *et al*, 2011) also found a statistically significantly higher MPI in ScH. In the study by (Ilic *et al*, 2013), as in our study, TSH positively correlates with MPI.

GLS is used to detect subclinical systolic dysfunction. It is considered a highly sensitive parameter. Its significance is greater in normal values of EF, as in this study. The displayed difference in S/TDI and GLS between the two analyzed groups is in favor of increased stiffness of the left ventricle in ScH. However, we need to keep in mind the fact that the values of GLS in both groups are within normal range. Two studies analyze this parameter in ScH. First, (Ilic *et al*, 2013) present a statistically significant difference in GLS between the examined and the control group. The average values of GLS (-20.4 ± 2.5, vs. -22.5 ± 2.1%) in the mentioned study have a higher negative value, in comparison to those in this study (-19.55 ± 2.3 vs. -20.9% ± 1.7%). Perhaps the selection of individuals in the control group in a tertiary health institution, and not volunteers as in the study by (Ilic *et al*, 2013) is the reason for the lower negative value of GLS in the control group in this study. Also, in the study of (Ilic *et al*, 2013) the both values of GLS are normal. The second study, (Sunbul *et al*, 2013), analyzes GLS in patients with untreated ScH, treated ScH and the control group (-17.3 ± 3.3, -19.0 ± 2.3 and -20.8 ± 2.9, respectively).In the study by (Sunbul *et al*, 2013) the average value of GLS in the control group was similar to the average value in this research, but the average value in untreated patients with ScH hasa lower negative value compared to the one in this study. The average TSH in patients with untreated ScH in the study by (Sunbul *et al*, 2013) (11.7mU/L) is also higher than the average value of TSH in this survey. The correlations showed a statistically significant negative correlation between TSH and GLS, and a positive one between fT4 and GLS. This means that with increasing of TSH, while reducing fT4, GLS gets a lower negative value. These results confirm the impact of ScH on global longitudinal left ventricular systolic function.

In only 2 patients in the group with ScH diastolic dysfunction were proved, versus none in the control group. The average age of patients with ScH in this study was 36, and it was 38 years in the control group. Although this difference did not prove to be statistically significant, still it examined relatively young patients, among which more time may be needed to develop systolic and diastolic dysfunction. It is certain that the joint presence of age and ScH will contribute to faster and greater deterioration of the parameter MPI, i.e. systolic and diastolic dysfunction of the left ventricle. Hypertension as the most common cause of diastolic dysfunction was the eliminating factor for entry into this study. The presence of ScH and hypertension would certainly increase the risk of developing diastolic dysfunction. Most of the patients analyzed had low levels of TSH, which leads to rapid detection of ScH, i.e. before possibly developing a diastolic dysfunction. It is probable that later detection of ScH could contribute to diastolic dysfunction. The results of the correlation of TSH with the parameters of diastolic dysfunction (negative correlation with the E/A ratio, and positive with E/e` sep.) speak in favor of this. Prospective, interventional, double blind study with a larger number of patients analyzed is needed for a more convincing proof of the impact of ScH on systolic and diastolic function of the left ventricle.

CONCLUSION

Subclinical hypothyroidism contributes to changes in certain parameters involved in the assessment of global and longitudinal systolic function, and diastolic left ventricular function compared to healthy individuals. The parameters which showed significant difference can help in monitoring patients.

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