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Kardiyak Resenkronizasyon Tedavisinin Ventriküler Repolarizasyon Parametreleri ve Ventriküler Aritmiler Üzerindeki Etkisi

Effect of Cardiac Resynchronization Therapy on Ventricular Repolarization Parameters and Ventricular Arrhythmias

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Öz

Giriş ve Amaç: Kardiyak re senkronizasyon tedavisi (KRT), sol ventrikül mekanik ve elektriksel dissenkronisi olan kalp yetmezliği (KY) hastalarında yaygın olarak kullanılmaktadır. KRT hastalarında sol ventrikül epikardiyal pacing, normal miyokardiyal aktivasyonu değiştirir ve repolarizasyonun transmural dağılımını arttırmaktadır. KRT'nin repolarizasyon parametreleri üzerindeki etkisini araştırmayı ve aritmik olaylar üzerindeki sonuçlarını ortaya çıkarmayı amaçladık.

Gereç ve Yöntemler: Çalışma, KRT ile tedavi edilen 54 hastadan oluşmaktaydı. Repolarizasyon parametreleri; QT, T tepeden T sonuna geçen süre (Tpe), JT, Tpe/QT, QT dispersiyonu ve Tpe disperisyonu ölçüldü. Hastalar ayrıca takip sonundaki ventriküler aritmi varlığına göre iki alt grupta incelendi. Alt gruplar repolarizasyon parametreleri açısından karşılaştırıldı. Başlangıç değerlerine göre repolarizasyon parametrelerinin değişimi de tüm grupta karşılaştırıldı.

Bulgular: Tüm çalışma grubunda akut fazda repolarizasyon parametrelerinin tamamı anlamlı olarak artmıştır. Kronik fazda, bu anormallikler önemli ölçüde azalmıştır. İki alt grubun karşılaştırılmasında ise repolarizasyon parametreleri açısından anlamlı bir fark saptanmamıştır.

Sonuç: Epikardiyal pacing, miyokardiyal repolarizasyon süresini uzatmakta ve repolarizasyonun transmural dağılımını arttırmaktadır. Ancak bu anormallikler geçici olup ventriküler aritmilerle ilişkili bulunmamıştır.

Anahtar kelimeler: Kalp yetmezliği, Kardiyak resenkronizasyon tedavisi, Yeni repolarizasyon parametreleri.

Abstract

Objective: Cardiac resynchronization therapy (CRT) is commonly used in patients with heart failure (HF) along with left ventricular mechanic and electrical dyssencrony. Left ventricular epicardial pacing in CRT patients changes the normal myocardial activation and increases the transmural dispersion of repolarization. We aimed to investigate the impact of CRT on repolarization parameters and reveal its consequences on arrhythmic events.

Materials and Methods: The study consisted of 54 patients treated with CRT. Repolarization parameters; QT, T peak-to-T end and JT, Tpe/QT, QT dispersion and Tpe dispersion were measured. The patients were also investigated in two subgroups according to the presence of ventricular arrhythmias at the end of follow-up. Subgroups were compared in terms of repolarization parameters.

Results The change in repolarization parameters according to baseline values were also compared in the whole group.In the whole study group, all of the repolarization parameters significantly increased in the acute phase. In the chronic phase, these abnormalities were significantly diminished. The comparison of the two subgroups did not show any significant difference in respect of repolarization parameters.

Conclusion: Epicardial pacing prolongs myocardial repolarization time and increases transmural dispersion of repolarization. However, these abnormalities were transient and were not associated with ventricular arrhythmias.

Keywords: Cardiac resynchronization therapy, Heart failure, New repolarization parameters.

1. Introduction

Cardiac resynchronization therapy (CRT) has become an established treatment modality to improve clinical symptoms, exercise tolerance and to reduce mortality, morbidity, and HF hospitalization in patients with mild to severe HF, reduced left ventricular ejection fraction (LVEF) and wide QRS complex [1,2]. Reversal of the normal myocardial activation sequence during epicardial pacing - as in CRT - increases the transmural dispersion of repolarization (TDR) [3, 4].

Increasing TDR, which is defined as the time difference of repolarization between mid-myocardial M cells and epicardial cells, decreases the net repolarization current and consequently prolongs the action potential time (APT). The APT prolongation occurs primarily in M cells, creating a vulnerable window along the ventricular wall.The decrease in net repolarization current also creates extrasystoles by causing early afterdepolarization (EAD) - induced triggered activity. Extrasystoles trigger the Torsades de pointes (TdP) by capturing the vulnerable window. The continuation of the arrhythmia is generally thought to be the result of circus movement reentry [5].

In patients with CRT-D, increased TDR measured with Tpeak-Tend (TpTe) and TpTe / QT has been associated with the incidence of ventricular arrhythmia [6]. In the 12-lead ECG, the TpTe interval is defined as the time measured from the peak of the positive T wave or the bottom of a negative T wave to the point where the isoelectric line crosses the tangent slope of the T wave (Figure 1).

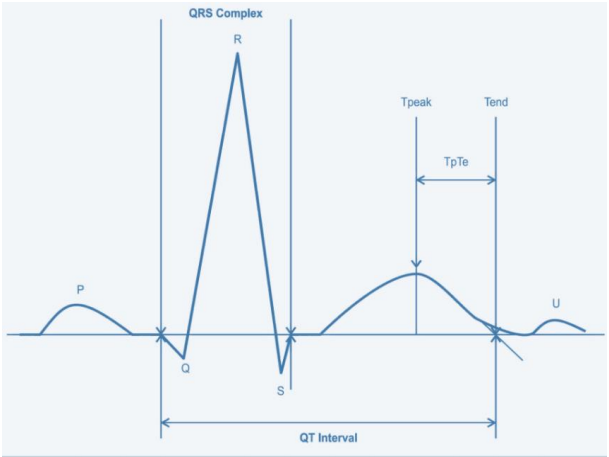

Figure 1. Electrocardiography parameters

TDR appears to play a major arrhythmogenesis role not only in patients with CRT, but also in patients with sudden cardiac arrest (SCA), ST segment elevation myocardial infarction, long QT syndrome and Brugada syndrome [7-10]. In a recent study, Tpec (TpTe corrected according to the Bazett formula) a more sensitive measurement in the assessment of the risk of sudden cardiac death (SCD), and Tpec > 90 ms was found to be associated with an approximately 3-fold increased risk [11].

CRT implantation fails in 5-10% of patients and approximately 30% of successful patients do not experience clinical improvement (non-responders) [12]. With transseptal endocardial LV pacing, CRT is an alternative for patients whose coronary vein anatomy is inappropriate, or the traditional CRT approach fails [13]. A more physiological activation is provided by stimulation of LV endocardium and potential arrhythmias can be prevented [14]. A multicentre prospective study involving 138 patients - ALSYNC (The ALternate Site Cardiac ResYNChronization) revealed that LV endocardial pacing (LVEP) is possible and reliable, but it is not known what happens if the electrode needs to be removed due to thromboembolic complications or infection [15]. In a small case-control study, a significant reduction in Tp-Te and QT dispersion values was found in the transpeptal LV endocardial lead implanted group compared to the coronary sinus (CS) group [16].

The extent and clinical significance of these repolarization abnormalities had not been fully elucidated. This study aimed to evaluate the effect of CRT on ventricular repolarization parameters and to determine whether these repolarization abnormalities are changed overtime. Furthermore, the relationship between arrhythmic events and these CRT-induced repolarization changes was also investigated.

2. Materials and Methods

This prospective study was conducted at the cardiology department with the permission of the local ethical committee and was carried out in accordance with the Declaration of Helsinki. 54 patients with successful biventricular pacemaker implantation due to standard CRT indication (QRS duration> 130ms regardless of morphology; LVEF ≤ 35%, New York Heart Association (NYHA) functional class II, III, and ambulatory IV despite optimal medical treatment (OMT), or patients requiring a ventricular pacing with a LVEF of ≤ 35% regardless of NYHA classification) were enrolled. None of the patients had a history of ventricular arrhythmia and other arrhythmic cardiac disorders. The only indication for CRT-D implantation has been considered as a primary prevention of sudden cardiac death

Device implantation was performed in the cardiac catheterization laboratory using local anesthesia and the standard transvenous approach of CRT implantation techniques. Following an apically right ventricular (RV) shock lead implantation, a quadripolar LV lead (Quartet Model 1458Q, St Jude Medical) and the right atrium (RA) lead were implanted.

12-lead ECGs were taken before CRT implantation, within 48 hours after the procedure, and 6 months after the procedure. All ECGs were scanned digitally and measurements were made at 400% magnification. The analysis was performed by a blinded cardiologist. While the beginning of the QT interval was considered as the first part (deflection) of the QRS complex, the end was considered as the point where the isoelectric line crosses the tangent slope of the T wave [17]. The longest interval of all leads wherein the T wave is clearly selected (usually V2 or V3) is considered the QT interval. The point J is defined as the point where the isoelectric ST segment begins and the QRS complex ends [18]. The obtained QT value was corrected using the "Bazzet formula" (QTc) [19]. the corrected JT (JTc) interval was calculated by subtracting QRS complex time from QTc interval (18). The TpTe interval was obtained from the difference between the QT interval and the QT peak interval. The QT peak interval was determined as the interval from the beginning of the QRS to the peak of the positive T wave or the bottom of a negative T wave [20]. In the case of a bimodal T wave, the first peak was chosen as a reference point. TpTe was averaged following calculating TpTe in all 12 leads [21]. Tpec was obtained from TpTe correction according to the Bazett formula [11]. The QT and TpTe dispersions were obtained from the difference between the longest and shortest of the mentioned intervals in 12-lead ecg [22].

Device records of all patients were analyzed. Details of the episodes were obtained from the device's clinical records and recorded electrograms. Device therapies were examined in two categories as shock or anti-tachycardic pacing (ATP). When both ATP and shock were applied in the same arrhythmia episode, the episode was evaluated in the shock category. Ventricular tachyarrhythmia, which was detected by the device and ended spontaneously without any therapy, was considered as non-sustained ventricular tachycardia (NSVT). Ventricular tachycardia (VT) or ventricular fibrillation (VF) episodes that meet the device detection criteria and undergo therapy were defined as sustained ventricular tachyarrhythmia (VTA) [23]. Having 3 or more VTA episodes within 24 hours was defined as an electrical storm [24]. Episodes that were delivered therapy due to supraventricular tachycardia (SVT) or atrial fibrillation (AF) were assessed as inappropriate and not included in the analysis. VTA detection criteria and therapy settings were programmed according to the nominal settings of the device when implanted and, if necessary, changed only in the opinion of the cardiologist.

2.1.Statistical analysis

Numerical variables were presented with mean and standard deviation (SD) values, while categorical variables were presented with frequency and percentages. In comparing the independent variables with the dependent variable, Mann Whitney U test was used because nonparametric conditions were provided for numerical variables. Paired samples t-test was used in comparison of numerical variables evaluated before, within 48 hours after procedure, and 6 months after the implantation of CRT. In all analyzes, $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 17.0 software (SPSS IBM, Chicago, IL, USA).

3. Results and Discussion

3.1.Results

54 patients with successful CRT implantation were included in the study. 39 (72.2%) of the patients were male and 15 (27.8%) were female. Mean age was 65.2 ± 11.6 with SD. Etiology of cardiomyopathy was linked to ischemic causes in 24 (44.4%) patients and non-ischemic causes in 30 (55.6%) patients. When the basal functional capacity (according to the NYHA classification) of patients were evaluated, it is seen that the majority (79.6%) was in the NYHA III classification. One patient was classified as NYHA I-II, one patient was NYHA II, four patients were classified as NYHA II-III, and five patients were classified as ambulatory NYHA IV.In basal rhythm evaluation; Six (11.1%) patients were in atrial fibrillation and 48 (88.9%) patients were in sinus rhythm. Basal morphology of 54 patients who underwent CRT was Left branch block (LBBB) for 52 (96.3%) patients and right branch block (RBBB) for 2 patients (3.7%). Baseline features of the patients are summarized in Table 1.

To analyse the acute effects of CRT on ventricular repolarization parameters, electrocardiographies were compared before the procedure and within 48 hours after implanting the CRT device, and it was found that Tpec and TpTe dispersion increased by an average of 11.68 ms and 10.54 ms, respectively (p values were <0.001 and 0.038, respectively). QTc, JTc, TpTe / QTc, and QT dispersion also increased, on average, by 37.28 ms, 55.10 ms, 0.0099, and 20 ms, respectively, in the acute phase (p values <0.001, <0.001, 0.034, <0.001, respectively). QRS duration decreased by an average of 16.64 ms in the acute phase with biventricular pacing and this decrease was statistically significant ($p < 0.001$) (Table 2).

When the electrocardiograms at baseline and after 6 months were compared, no statistically significant difference was found in Tpec, TpTe dispersion, QTc, TpTe / QTc and QT dispersion compared to the preprocedure, and the changes detected in the acute phase were found to be transient (p values> 0.05). Decrease in QRS duration persisted on ECGS at the 6th month, and that QRS duration decreased by an average of 16.59 ms compared to baseline ($p < 0.001$). In the 6th month, the persistence of the decrease in QRS time without a significant change in QTc resulted in an average increase of 22.09 ms of JTc, one of the ventricular repolarization parameters ($p < 0.001$) (Table 2). Figure 2 shows the acute and long-term effect of Cardiac Resynchronization Therapy on Tp-Te interval, as an example of ventricular repolarization parameters.

Table 1. Baseline characteristics of the study patients

		Patients implanted with CRT (n = 54)
Age, years		65.2±11.6
Gender	Male (%)	39 (72.2)
	Female (%)	15 (27.8)
Etiology	Ischemic (%)	24 (44.4)
	Non-ischemic (%)	30 (55.6)
NYHA functional class	I-II (%)	1 (1.9)
	II (%)	1 (1.9)
	II-III (%)	4 (7.4)
	III (%)	43 (79.6)
	Ambulatory IV (%)	5 (9.3)
Baseline rhythm	AF (%)	6 (11.1)
	SR (%)	48 (88.9)
QRS morphology	LBBB (%)	52 (96.3)
	RBBB (%)	2 (3.7)
Device	CRT-D	54(100)
	CRT-P	0
LVEF, %		23.5±5.9
DM		15 (28)
HT		37 (69)
Drugs	ACE-I/ARB	54 (100)
	Beta blocker	45 (83)
	MRA	30 (56)
	Amiodarone	2 (3.7)
	Digoxin	5 (9.3)

ACE-I - angiotensin-converting enzyme inhibitor; AF - atrial fibrillation; ARB - angiotensin II receptor blocker; DM - diabetes mellitus; HT - hypertension; LVEF - left ventricular ejection fraction; LBBB - left bundle branch block; MRA – mineralocorticoid receptor antagonist; NYHA - New York Heart Association; RBBB - bundle branch block. Values are described as n (%) or mean±standard deviation.

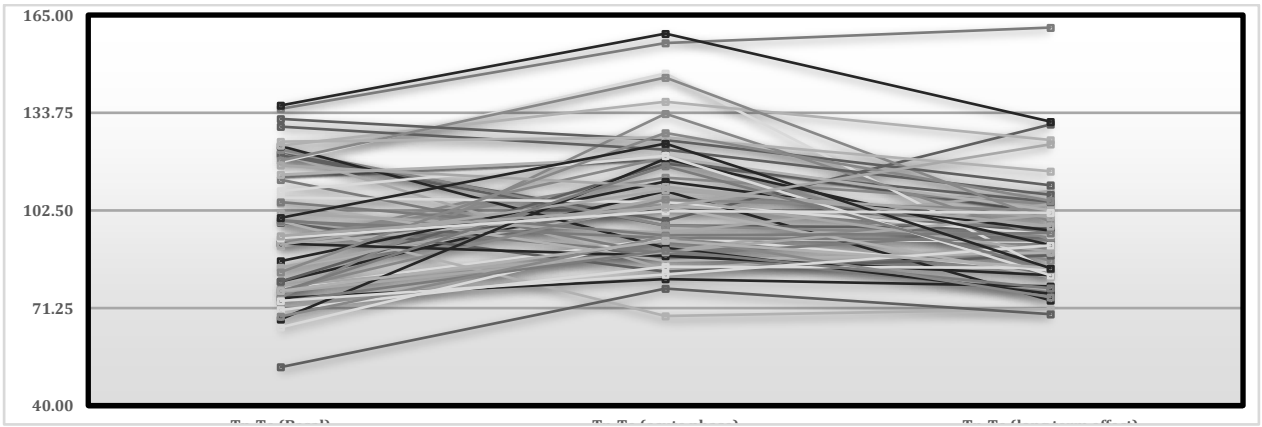

Figure 2. The acute and long-term effect of CRT Therapy on TpTe interval, as an example of ventricular repolarization parameters

Table 2. Effect of cardiac resynchronization therapy on ventricular repolarization parameters

	Baseline value (mean±SD)	**Acute phase value (within 48 hours) (mean±SD)**	**Values after 6 months (mean±SD)**
QTc (ms)	537.30±49.21	574.58±42.92 **P<0.001**	538.16±45.41 P=0.917
JTc (ms)	351.92±37.39	407.02±33.68 **P<0.001**	374.01±33.57 **P<0.001**
Tpec (ms)	106.03±20.39	117.70±20.33 **P<0.001**	104.06±19.40 P=0.501
TpTe/QTc	0.18±0.03	0.19±0.04 **P=0.034**	0.18±0.03 P=0.423
QT dispersion (ms)	82.51±29.43	102.51±34.96 **P<0.001**	95.72±87.32 P=0.266
TpTe dispersion (ms)	70.79±31.93	81.33±24.76 **P=0.038**	68.18±20.19 P=0.586
QRS duration (ms)	165.29±21.20	148.65±19.99 **P<0.001**	148.70±19.07 **P<0.001**

JTc – JT corrected (Difference between QT corrected and QRS interval); QTc - QT corrected; Tpec – TpTe corrected; TpTe - Difference between QT and QT peak interval.
The repolarization parameters were compared using paired samples t-test

Our mean follow-up was 17.7 months (interquartile range: 12.6-31.2). Ventricular tachyarrhythmia (VTA) episode occurred in 24 (44.4%) of the patients. Sustained VTA occurred in 14 (25.9%) patients, ATP in 8 (14.8%) patients, shock in 6 (11.1%) patients, and NSVT in 19 (35.2%) patients. The average number of episodes in 24 patients with VTA episodes was 7.9 ± 15.03. In 5 patients (9.25%), ≥ 3 arrhythmia episodes were observed within 24 hours and evaluated as an electrical storm. In terms of early ventricular repolarization parameters after CRT, no significant difference was observed between patients with VTA episodes and those without (p values> 0.05) (Table 3).

Table 3. Effect of cardiac resynchronization therapy on ventricular arrhythmias in respect of repolarization parameters.

Acute phase parameter (within 48 hours)	**Group 1 (with VTA) (n=24)**	**Group 2 (with no VTA) (n=30)**	**P value**
QTc (ms)	574.82±48.99	574.38±38.24	0.969
JTc (ms)	405.82±37.80	407.98±41.55	0.844
Tpec (ms)	122.92±24.07	113.53±15.97	0.092
TpTe/QT	0.195±0.04	0.186±0.04	0.440
QT dispersion (ms)	99.24±37.21	105.14±33.46	0.543
Tpe dispersion (ms)	82.19±28.11	80.63±22.21	0.820

JTc – JT corrected (Difference between QT corrected and QRS interval); QTc - QT corrected; Tpec – TpTe corrected; TpTe - Difference between QT and QT peak interval; VTA - ventricular tachyarrhythmia.

3.2.Discussion

Cardiac resynchronization therapy (CRT), which constitutes an important hope for heart failure, is concerned that it may be proarrhythmic as pacing in the epicardium increases transmural dispersion of repolarization [3,4]. The aim of the present study was to investigate the effect of CRT on ventricular repolarization parameters overtime and to determine whether these repolarization abnormalities are related to arrhythmic events. The main findings we have revealed can be summarized as follows.

(i) The ventricular repolarization parameters significantly increased in the acute phase following CRT implantation

(ii) In the chronic phase, these abnormalities were significantly disappeared.

(iii) Patients with ventricular tachyarrhythmia (VTA) did not show any significant difference in respect of repolarization parameters compared to those without VTA

The normal myocardial activation sequence reverses in conventional CRT patients. Fish et al. showed that early repolarization of epicardium, a consequence of this reverse activation, delayed activation and repolarization of mid-myocardial M cells caused a marked increase in QT interval and TDR [4]. Increased TDR can be measured by noninvasive parameters such as Tpeak Tend (TpTe or Tpe), TpTe corrected according to the Bazzet formula (Tpec) and Tp-Te / QT [4,6]. While the prolongation of the QT Interval covering the periods of ventricular depolarization and repolarization increases the risk of arrhythmia, the increased QRS duration in patients with branch block causes QT prolongation because it includes ventricular depolarization.The use of the JT interval is recommended for appropriate ventricular repolarization measurement in such patients (25). In some studies, the QT dispersion which shows regional heterogeneity in myocardial repolarization and obtained by calculating the difference between the longest and the shortest QT intervals on 12-lead ECG, is associated with life-threatening arrhythmias and SCD. In a meta-analysis involving 14 studies investigating the effects of resynchronization therapy on ventricular repolarization, biventricular pacing had no apparent effect on QT, JT and TpTe, and contrary to what Gold et al. [27] showed, a slight decrease in QT dispersion values [significance was uncertain; $p = 0.05$] was detected. However, the same analysis showed that LV pacing does not affect QT, JT, and QT dispersion values, but only increases TpTe [25]. Nevertheless, TpTe has been proved to be superior to QT and QT dispersion in predicting ventricular arrhythmias [24,25].

Our observation regarding the effects of CRT on ventricular repolarization patterns is consistent with that in a study conducted by Itoh et al., supporting that the increase in TpTe, which was observed 1 week after CRT implantation, gradually decreased over 6 and 12 months, and consequently they revealed that the transmural dispersion was temporally affected [23,24]. Differently, we measured Tpec, which is considered more precise than TpTe, and evaluated the effects of CRT on many different ventricular repolarization parameters, and our results were found to be compatible. Similar results were proved in another study that in addition showed no significant difference between the groups in terms of ventricular tachyarrhythmic events according to the changes in TpTe values detected in the acute phase, which supports our findings [21]. Although these transient changes are not fully elucidated, they are considered related to mechanical reverse remodelling [25,26]. As shown in various experimental studies, CRT corrects changes in gene expression (particularly stress-induced kinases and cytokines) induced by electromechanical dyssynchrony, restores abnormal calcium hemostasis and reduces regional heterogeneity of action potential duration [21,26].

Other mechanisms that may explain the proarrhythmic effects of CRT have been proposed. According to a study conducted by Roque et al., They associated CRT-induced proarrhythmia with re-entran VTAS within the epicardial scar tissue area of Left ventricular (LV) pacing and successfully treated with catheter ablation [23-26]. Whereas Mykytsey et al. suggested that LV pacing's proarrhythmic mechanism depends on one-way block and reentry by changing the activation sequence within the scar areas [27]. On the other hand, in many studies there was a significant decrease in ventricular tachyarrhythmia in patients who responded to CRT, while an increase in ventricular tachyarrhythmias was observed in patients who did not respond [23-26]. It has been suggested that these antiarrhythmic properties of CRT can be explained by CRT's LV reverse remodeling, electrical stabilization of myocyte membranes, and a decrease in myocardial wall stress [27]. The fact that the VTAs observed in our study were not affected by the temporal change in the ventricular repolarization parameters in the acute phase supports the antiarrhythmic feature of CRT.

Study limitations

We have to acknowledge that the most important limitation of our study is that our patient sample size is relatively small. Therefore, it should be supported by larger studies to generalize our observations. Another limiting factor is the relatively high ischemic etiology (44.4%) enrolled in the study. The presence of ischemic scars and the heterogeneity of the myocardium may have affected arrhythmic events.Furthermore, given the nature of the study, we cannot ignore the effect of extrinsic and intrinsic patient variables such as coronary anatomy and LV lead position on outcomes.

4. Conclusion

Successful cardiac resynchronization therapy (CRT) affects depolarization by narrowing the QRS duration both in the acute phase and in the long term. Epicardial pacing in conventional CRT prolongs myocardial repolarization time and increases the transmural dispersion of repolarization (TDR) significantly measured with Tpec, TpTe dispersion, TpTe / QTc and QT dispersion. However, these repolarization

abnormalities were transient and disappeared overtime and were not significantly associated with ventricular tachyarrhythmias. The small size of our study group may be a limiting factor and larger studies are required to generalize the results.

5. Acknowledgments and disclosures

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