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SHORT REPORT

Right ventricular outflow tract diameter change with exercise: a prospective exercise echocardiography and invasive CPET study

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Abstract

While cardiac output reserve with exercise predicts outcomes in cardiac and pulmonary vascular disease, precise quantification of exercise cardiac output requires invasive cardiopulmonary testing (iCPET). To improve the accuracy of cardiac output reserve estimation with transthoracic echocardiography (TTE), this prospective study aims to define changes in right ventricular outflow tract diameter (RVOTd) with exercise and its relationship with invasively measured haemodynamics. Twenty subjects underwent simultaneous TTE and iCPET, with data collected at rest, leg-raise, 25 W, 50 W ($n = 16$), 75 W ($n = 14$), and 100 W ($n = 6$). This was followed by a second exercise study with real-time RV pressure–volume loops at similar stages (except leg-raise). The overall cohort included heart failure with preserved ejection fraction ($n = 12$), pulmonary arterial hypertension ($n = 5$), and non-cardiac dyspnoea ($n = 3$). RVOTd was reverse engineered from the TTE-derived RVOT velocity time integral (VTI) and iCPET-derived stroke volume, using the formula: Fick stroke volume = RVOT VTI × RVOT area (wherein RVOT area = $\pi \times$ [RVOTd/2]2). RVOTd increased by nearly 3–4% at every 25 W increment. Using linear regression models, where each subject is treated as a categorical variable and adjusting for subject intercept, RVOTd was correlated with haemodynamic variables (cardiac output, heart rate, pulmonary artery and RV pressures). Of all the predictor haemodynamic variables, cardiac output had the highest $r2$ model fit (adjusted $r^2 = 0.68$), with a unit increase in cardiac output associated with a 0.0678 increase in RVOTd ($P < 0.001$). Our findings indicate that RVOTd increases by 3–4% with every 25 W increment, predominantly correlated with cardiac output augmentation. These results can improve the accuracy of cardiac output reserve estimation by adjusting for RVOTd with graded exercise during non-invasive CPET and echocardiogram. However, future studies are needed to define these relationships for left ventricular outflow tract diameter.

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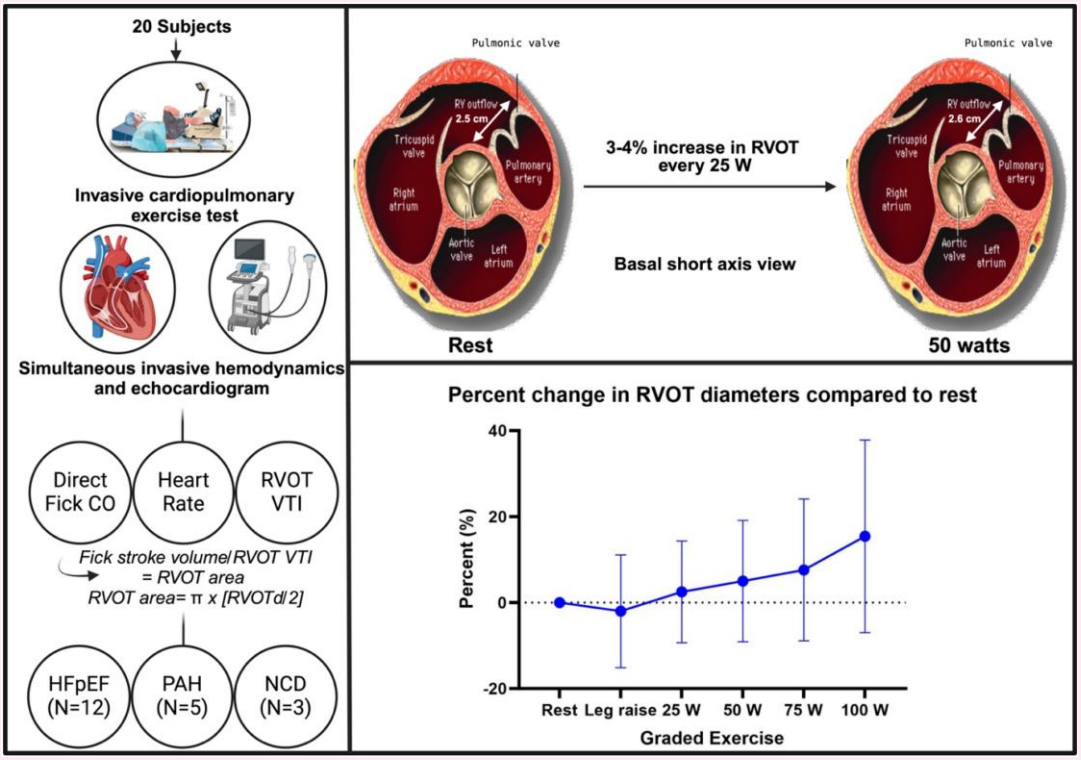
Graphical Abstract



CO, cardiac output; RVOT, right ventricular outflow tract; VTI, velocity time integral; HFpEF, heart failure with preserved ejection fraction; PAH, pulmonary arterial hypertension; NCD, non-cardiac dyspnoea.

Keywords right ventricular outflow tract diameter • cardiopulmonary exercise testing • cardiac output • exercise haemodynamics

Cardiac output augmentation with exercise (cardiac reserve) defines normal cardiopulmonary function in health and disease.[1,2] In early disease stages of pulmonary hypertension (PH) or heart failure, poor cardiac reserve can lead to exercise intolerance.[3] For precise quantification of cardiac reserve and assessment of multi-system contributors to exercise intolerance, invasive cardiopulmonary testing (iCPET) is the gold standard method.[4] While iCPET facilities are limited worldwide, exercise testing with transthoracic echocardiogram (TTE) and non-invasive CPET are widely available.[5] However, cardiac output assessment via TTE with exercise is reported to be underestimated,[6] which may be due to unaccounted change in ventricular outflow tract area with exercise.

iCPET studies have shown that with exercise, cardiac output can increase by 2-fold and stroke volume can increase by nearly 30%.[7,8] While this increase in flow can impact ventricular dimensions with exercise, there are limited data available on the correlation between right ventricular outflow tract diameter (RVOTd) and graded exercise, as well as the relationship between RVOTd and invasively measured haemodynamic parameters. We hypothesize that RVOTd increases proportional to incremental workload during exercise, primarily driven by cardiac output augmentation.

To test this hypothesis, we prospectively enrolled 20 subjects who underwent simultaneous TTE and iCPET on a semi-recumbent ergometer. Haemodynamic data points were acquired at rest, leg-raise (except pulmonary artery pressure), 25 W ($n = 20$), 50 W ($n = 16$), 75 W ($n = 14$), and 100 W ($n = 6$). RVOT pulse wave Doppler (PWD) waveform from TTE was used to acquire velocity time integral (VTI) data at rest and with exercise stages. RVOT VTI data were only included in analyses if signal quality was adequate, and 3–5 beats were available at each stage to take the average VTI. Afterwards, subjects had a rest for 15–30 min and then performed a second round of exercise. During the second round with similar stages of rest-to-exercise (except passive-leg-raise stage), high fidelity conductance-based real-time right ventricular pressure–volume loops were obtained with the Inca pressure–volume loop system (CD Leycom, Hengelo, Netherlands). The overall cohort included three groups: heart failure with preserved ejection fraction—HFpEF ($n = 12$), pulmonary arterial hypertension—PAH ($n = 5$), and non-cardiac dyspnoea (NCD) with subjective dyspnoea but no rest or exercise PH ($n = 3$). Baseline characteristics were compared using χ^2 or Fisher's exact test for categorical variables. Continuous variables were compared with ANOVA or Kruskal–Wallis test. Direct Fick cardiac output and stroke volume were obtained from iCPET. RVOTd was reverse engineered from the TTE-derived RVOT VTI and iCPET-derived stroke volume, using the formula: Fick stroke volume = RVOT VTI × RVOT area (wherein RVOT area = $\pi \times$ [RVOTd/2]2).[5,6] Paired observations were compared by paired *t*-test between RVOTd at rest and subsequent stages in the protocol (leg-raise, exercise stages). The association of change in RVOTd with predictors [cardiac output, heart rate, mean pulmonary artery pressure (mPAP), right ventricular systolic pressure (RVSP), and end-diastolic pressure (RVEDP)] was investigated through linear regression models (or ANCOVA models) adjusting for subject intercept, in which each subject was treated as a categorical variable. Workload was not included as a separate variable in the model as we assume it drove variability

in the predictor variables. The slope of RVOTd and the predictor was an estimate of change in RVOTd given change in one unit of the predictor, within individuals. $r2$ and $r2$ adjusted for the number of parameters and observations were included in the tables for a comparison of model fit.

In overall cohort, the mean age was 64 ± 12 years, BMI 31.2 ± 4.9 kg/m^2, and 60% were females. Baseline characteristics were comparable between the groups except for a trend of higher prevalence of systemic hypertension and atrial fibrillation in the HFpEF group (*Table 1*). In comparison to the NCD group, HFpEF and PAH subjects had worse exercise capacity and ventilatory efficiency. Metrics of right and left ventricular function at rest were comparable among the three groups (*Table 1*). In the overall cohort, with different stages (rest, leg-raise, 25 W, 50 W, 75 W, 100 W), cardiac output (L·min^{-1}) increased: 5.58 ± 1.48, 5.66 ± 1.82, 8.21 ± 2.73, 9.0 ± 2.1, 11.0 ± 2.66, and 12.0 ± 3.63. Stroke volume (mL) increased: 79.8 ± 19.8, 77.8 ± 22.7, 90.4 ± 23.8, 90.2 ± 20.2, 96.9 ± 22.2, and 94.1 ± 32.7. Heart rate increased: 70.4 ± 10.0, 73.2 ± 11.7, 90.3 ± 13.3, 100.0 ± 12.4, 113.6 ± 15.1, and 124.2 ± 15.1. With echocardiogram, RVOT VTI (cm) was: 16.6 ± 3.5, 15.9 ± 3.5, 17.0 ± 3.8, 16.8 ± 4.3, 16.6 ± 4.6, and 14.1 ± 3.2, peak velocity (m/s) was: 0.75 ± 0.17, 0.83 ± 0.08, 0.90 ± 0.22, 0.94 ± 0.22, 0.83 ± 0.08, and 0.90 ± 0.20, and peak gradient (mmHg) was: 2.5 ± 1.1, 2.9 ± 1.2, 3.4 ± 1.7, 3.6 ± 1.8, 2.8 ± 0.7, and 3.5 ± 1.3. The pressure data were missing with the passive-leg-raise stage. However, in a similar trend (rest, 25 W, 50 W, 75 W, 100 W), mPAP (mmHg) increased: 30.3 ± 8.7, 45.8 ± 8.4, 45.9 ± 6.0, 50.4 ± 7.5, and 52.0 ± 7.8. RVSP (mmHg) increased: 34.6 ± 14.5, 51.0 ± 17.6, 48.7 ± 12.6, 54.1 ± 9.9, and 55.8 ± 11.5. RVEDP (mmHg) increased: 7.4 ± 3.7, 13.9 ± 5.9, 13.4 ± 6.6, 16.0 ± 7.8, and 14.9 ± 7.1.

The increase in RVOTd with exercise is represented in *Figure 1*. In comparison to rest (2.53 ± 0.36 cm), the increase in RVOTd approached statistical significance at 75 W (2.76 ± 0.32 cm; $P = 0.06$) and 100 W (2.99 ± 0.62 cm; $P = 0.08$) (*Figure 1A*). Overall, comparing the per cent change in RVOTd from rest–25 W and consecutive exercise stages, RVOTd increased by almost 3–4% every 25 W (*Figure 1B*). At high workload (100 W), the diameter increased by 15%, in comparison to rest values ($n = 6$, which included three HFpEF, two PAH, and one NCD subjects). Increases in cardiac output, heart rate, mPAP, RVSP, and RVEDP were all associated with increases in RVOTd in univariate models adjusting for subject intercept (*Table 2*). Of the predictor variables, cardiac output had the highest $r2$ model fit (adjusted $r2 = 0.68$, $P < 0.001$) and a unit increase in cardiac output was associated with a 0.0678 increase in RVOTd (*Table 2*). Relationship of RVOTd was weaker with heart rate and pressure data (as shown by a flatter slope and lower β-estimate values, *Table 2*). As RVOTd was computed from stroke volume, these variables are associated by definition and hence, stroke volume was not included in regression analyses.

Our findings revealed a progressive 3–4% increase in RVOTd at every incremental 25 W workload. This increase in RVOT diameter showed the strongest correlation and positive slope with augmentation in cardiac output with exercise. In comparison to cardiac output, heart rate and pressures (mPAP, RVSP, and RVEDP) had less strong relationships with the increase in RVOTd. These results suggest that cardiac output is the most significant contributor to increased RVOTd with exercise. However, the haemodynamic factors that contribute to increased RVOTd with incremental exercise are likely more complex and may vary at different stages of disease and with different disease subtypes. For example, in advanced stages of disease (e.g. HFpEF or PAH), cardiac output augmentation with exercise can be severely blunted[9] and RV pressure changes may become a predominant factor. In other words, a heterometric response of the right ventricle could be expected in health and early disease, wherein right ventricular size (and RVOTd) increases with an increase in cardiac output. However, in advanced disease, homeometric adaptation may take over, resulting in increased wall stress and contractility without further dilation (as heterometric adaptation becomes exhausted).[10]

Another key observation based on studies by van Riel *et al.*[11] and Wright *et al.*[12] is that with exercise, a gradient develops between RVOT and pulmonary artery (PA) in an upright position, which possibly indicates dynamic RVOT obstruction or increased valve flow. Specifically, Wright *et al.* study supports the increased valve flow as a more likely explanation of this RVOT gradient. These findings could impact the echocardiogram-based Doppler estimation of flow across RVOT, as an increase in RVOT-PA gradient would lead to an increased VTI by continuous wave Doppler. Our study did not capture this information, as we did not record RV and PA pressures simultaneously on cardiac catheterization and RVOT continuous wave Doppler on echocardiogram. However, in our study, the peak velocities and gradient on

Table 1 Baseline characteristics

Baseline characteristics	Overall cohort ($n = 20$)	HFpEF ($n = 12$)	PAH ($n = 5$)	NCD ($n = 3$)	*P*-value
Age, years	63.5 ± 11.9	66.9 ± 6.3	59.5 ± 16.7	56.7 ± 19.9	0.61
Body mass index, kg/m^2	31.2 ± 4.9	32.5 ± 4.6	30.0 ± 6.4	30.0 ± 3.4	0.80
Female, *n* (%)	12 (60)	5 (42)	4 (80)	3 (100)	0.18
Hypertension, *n* (%)	15 (75)	11 (92)	3 (60)	1 (33)	0.06
Dyslipidaemia, *n* (%)	14 (70)	9 (75)	4 (80)	1 (33)	0.41
Diabetes mellitus, *n* (%)	7 (35)	6 (50)	4 (80)	1 (20)	0.22
Atrial fibrillation, *n* (%)	7 (35)	6 (50)	0 (0)	1 (33)	0.16
CAD, *n* (%)	6 (30)	4 (33)	2 (40)	0 (0)	0.64
CKD, *n* (%)	3 (15)	3 (25)	0 (0)	0 (0)	0.71
COPD, *n* (%)	2 (10)	2 (17)	0 (0)	0 (0)	0.99
LVEF, %	62.4 ± 3.6	62.2 ± 4.4	62.0 ± 2.4	63.7 ± 3.2	0.83
TAPSE, cm	2.0 ± 0.5	2.1 ± 0.5	1.7 ± 0.4	2.4 ± 0.1	0.16
Peak VO_2, mL/kg/min	13.7 ± 5.7	12.4 ± 3.9	12.8 ± 3.9	20.5 ± 10.7	0.36
V_E/VCO_2 slope	37 ± 8	38 ± 8	40 ± 6	31 ± 8	0.37

HFpEF, heart failure with preserved ejection fraction; PAH, pulmonary arterial hypertension; NCD, non-cardiac dyspnoea; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; RVOT, right ventricular outflow tract; VTI, velocity time integral; TAPSE, tricuspid annular plane systolic excursion; VO_2, oxygen consumption; V_E/VCO_2, minute ventilation to carbon dioxide production.

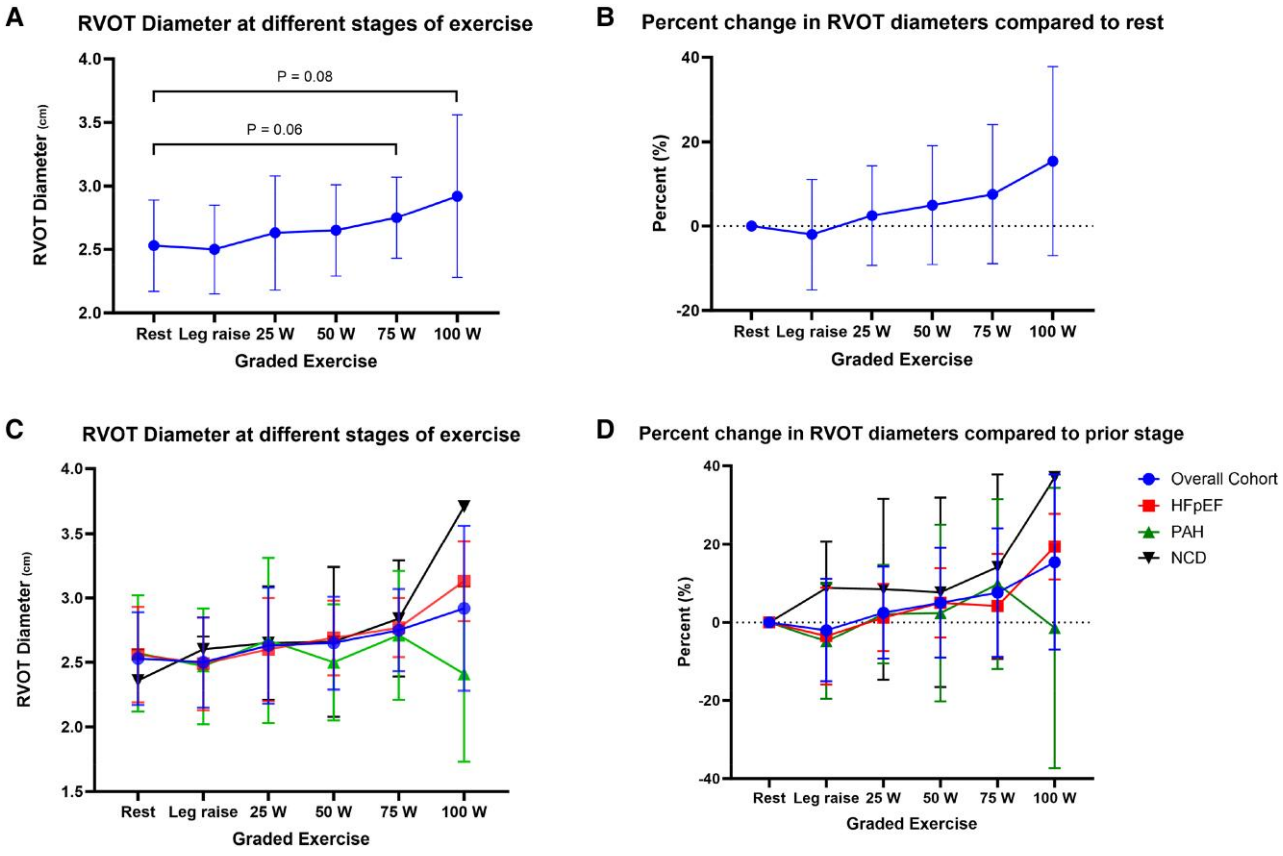


Figure 1 Change of RVOT diameter at different workloads in the overall cohort (*A*. RVOT diameter in cm, and *B*. percent change in RVOT diameter) and the three subgroups (*C*. RVOT diameter in cm, and *D*. percent change in RVOT diameter). Reported as mean ± standard deviation. *P*-values comparing RVOT diameter at rest and exercise stage. RVOT, right ventricular outflow tract; HFpEF, heart failure with preserved ejection fraction; PAH, pulmonary arterial hypertension; NCD, non-cardiac dyspnoea.

RVOT PWD did not increase significantly with exercise, which possibly suggests absence of significant RVOT gradient. We interpret these findings with caution due to the above-mentioned limitations of our study, however the likely explanation is the different body position e.g. semi-recumbent in our study and upright (or semi-upright) in prior studies. This is particularly the case as van Riel study reported that RVSP-PASP gradient occurs as subjects were moved from a rest supine position to a rest upright position (even before exercise). Hence, our findings of RVOT diameter change with exercise can only be applied if exercise is performed in a supine or semi-recumbent position (non-upright). Future studies are needed to determine the relationship of RVOT dimensions with RVOT-PA gradients with exercise, ideally with a cardiac MRI and MRI-compatible pressure transducers.

This study is limited by its modest size and inclusion of three pathophysiological cohorts. Additionally, the sample size at higher workloads (75 W and 100 W) was even lower due to combination of limited patient effort and exclusion due to limited echocardiographic windows (poor quality RVOT signal or inaccurate sample volume). Nonetheless, this is the first study to demonstrate a quantified change in RVOTd with incremental workload and report a correlation between RVOTd with cardiac output during graded exercise, which provides clinically relevant information for exercise echocardiogram-based laboratories. We also note the absence of passive-leg-raise stage for pressure data, which may impact the strength of correlation with regression analyses in this study. These findings need to be validated in prospective studies with larger sample size that demonstrate our suggested increase in per cent RVOTd with graded exercise leading to better cardiac output estimations in healthy subjects and different disease groups. Inter-subject and inter-group (HFpEF, PAH, NCD) variability of these findings remains a limitation, which we addressed with subject-specific regression model. Additionally, lack of left ventricular outflow tract (LVOT) VTI in this study limits any extrapolation of these findings to LVOT diameter that is possibly less prone to dilatation with more rigid left heart structures. Lastly, a technical limitation is a possible sampling error of RVOT VTI signal if the sample volume is placed a few mm more upstream of the annulus during exercise. To reduce this possible error, we only included RVOT VTI data with adequate signal quality and 3–5 beats available at each stage, which were averaged. Overall, these findings should be taken as proof of concept from a pilot study, and it would be critical to choose one consistent exercise modality for future validation studies.

In summary, our study demonstrates that RVOTd increases by 3–4% every 25 W on a semi-recumbent ergometer and is associated with an increase in cardiac output in a small cohort of 20 subjects. These findings suggest that including RVOTd at rest and adjusting for increase in RVOTd with incremental exercise stages during stress echocardiogram can provide a more accurate measure of cardiac output from rest-to-exercise. Further larger studies are needed to validate these findings in healthy subjects and different disease groups, ideally with simultaneous LVOT and RVOT VTIs with exercise echocardiography or cardiac MRI.

Table 2 Correlations of RVOT diameter and haemodynamic parameters

	β-Estimate	Standard error of β-estimate	*P*-value	r^2	Adjusted r^2
Cardiac output	0.0678	0.009	<0.001	0.75	0.68
Heart rate	0.0074	0.0015	<0.001	0.68	0.60
mPAP	0.0097	0.0036	0.01	0.72	0.60
RVSP	0.0082	0.0025	0.002	0.74	0.64
RVEDP	0.0152	0.0070	0.036	0.72	0.60

Adjusted for subject intercepts $n = 20$.
mPAP, mean pulmonary artery pressure; RVSP, right ventricular systolic pressure; RVEDP, right ventricular end-diastolic pressure.

Consent

All subjects provided informed consent in agreement with guidelines approved by the UW-Madison institutional review board (IRB ID: 2019-1184). The study complied with the guidelines of Declaration of Helsinki and was overseen by an independent safety and monitoring board.

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Conflict of interest: None declared.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Lead author biography

Farhan Raza is an early-career heart failure and pulmonary hypertension cardiologist with research focus on vascular mechanics and invasive exercise haemodynamics. He is the director of invasive cardiopulmonary exercise test laboratory and associate director of Pulmonary Hypertension programme at University of Wisconsin—Madison. With current support, including career development awards from the AHA and NIH, his research studies are focused on bioengineering vascular mechanics, cardiac MRI 4D flow, and bioinformatics analyses of multiomics studies of myocardial tissue in HFpEF (heart failure with preserved ejection fraction).

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