Impact of Atrial Fibrillation on Exercise Capacity in Heart Failure With Preserved Ejection Fraction

A RELAX Trial Ancillary Study

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Background—Atrial fibrillation (AF) is common among patients with heart failure and preserved ejection fraction (HFpEF), but its clinical profile and impact on exercise capacity remain unclear. RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in HFpEF) was a multicenter randomized trial testing the impact of sildenafil on peak VO₂ in stable outpatients with chronic HFpEF. We sought to compare clinical features and exercise capacity among patients with HFpEF who were in sinus rhythm (SR) or AF.

Methods and Results—RELAX enrolled 216 patients with HFpEF, of whom 79 (37%) were in AF, 124 (57%) in SR, and 13 in other rhythms. Participants underwent baseline cardiopulmonary exercise testing, echocardiogram, biomarker assessment, and rhythm status assessment before randomization. Patients with AF were older than those in SR but had similar symptom severity, comorbidities, and renal function. β-blocker use and chronotropic indices were also similar. Despite comparable left ventricular size and mass, AF was associated with worse systolic (lower EF, stroke volume, and cardiac index) and diastolic (shorter deceleration time and larger left atria) function compared with SR. Pulmonary artery systolic pressure was higher in AF. Patients with AF had higher N-terminal pro-B-type natriuretic peptide, aldosterone, endothelin-1, troponin I, and C-telopeptide for type I collagen levels, suggesting more severe neurohumoral activation, myocyte necrosis, and fibrosis. Peak VO₂ was lower in AF, even after adjustment for age, sex, and chronotropic response, and V̇ₐ/VO₂ was higher.

Conclusions—AF identifies an HFpEF cohort with more advanced disease and significantly reduced exercise capacity. These data suggest that evaluation of the impact of different rate or rhythm control strategies on exercise tolerance in patients with HFpEF and AF is warranted.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00763867.

Impact of Atrial Fibrillation on Exercise Capacity in Heart Failure With Preserved Ejection Fraction

Atrial fibrillation (AF) and heart failure (HF) commonly coexist and the presence of each worsens the outcome of the other.¹ The prevalence of AF in HF with preserved left ventricular ejection fraction (HFpEF; LVEF≥50%) is similar to that observed in patients with HF and reduced EF (HFrEF).² In HFpEF, patients with AF have worse exercise capacity than those in sinus rhythm (SR),³ and small studies suggest that rhythm control improves exercise capacity.⁴⁺ However, patients with HFpEF have been under-represented in AF studies and it remains unclear whether the presence of AF further compromises exercise performance in HFpEF. Likewise, there is limited information on the profile of the patient with HFpEF and AF, particularly in stringently defined HFpEF subjects with truly normal LVEF.⁷

Clinical Perspective on p 130

The RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in HFpEF) trial enrolled 216 patients with HFpEF who met rigorous entry criteria designed to ensure the presence of HF and cardiac limitation to exercise.⁸ Rhythm status, echocardiography, biomarker assessment, and cardiopulmonary exercise testing (CPXT) were performed at baseline. We hypothesized that HFpEF patients with AF would display more advanced HF and greater...
impairment of exercise capacity when compared with HFpEF patients in SR. As HFpEF is associated with chronotropic incompetence,9 while patients with AF display an increased heart rate (HR) response during exercise,10 we also evaluated the relationship between rhythm status and chronotropic response during exercise in HFpEF.

Methods
RELAX was a multicenter randomized (1:1) placebo-controlled trial testing the impact of chronic PDE5 (phosphodiesterase 5) inhibition (sildenafil) on exercise capacity in patients with HFpEF.7 The trial was conducted by the Heart Failure Clinical Research Network (HFN) and funded by the National Heart, Lung, and Blood Institute. All patients provided written informed consent and the trial was approved by the institutional review board at each participating site. Notably, sildenafil did not improve exercise capacity in HFpEF patients in RELAX and there was no evidence of an interaction between sildenafil and rhythm status.8

Study Participants
RELAX enrolled patients with objective evidence of HF, LVEF ≥50%, reduced exercise capacity, as evidenced by reduced (≤50% predicted) peak oxygen consumption (peak VO2) at screening CPXT11 and evidence of elevated filling pressures (elevated pulmonary capillary wedge pressure measured invasively or N-terminal pro-B-type natriuretic peptide ≥400 pg/mL). Additional entry criteria have been reported previously.3 Rhythm status was classified as rhythm present on baseline electrocardiography. A history of AF was also recorded.

Baseline Studies
The RELAX study design has been reported previously.6,12 Pertinent to this analysis, patients underwent baseline transthoracic echocardiography performed according to a standard protocol15 with measurements performed at the HFN echocardiography core laboratory (Mayo Clinic, Rochester, MN). Values reported in AF represent an average of 3 to 5 beats. Plasma biomarker measurement included markers of neurohumoral activation (aldosterone, N-terminal pro-B-type natriuretic peptide, endothelin-1), cardiac injury or inflammation (troponin I, C-reactive peptide), renal function (cystatin C, uric acid), and fibrosis (procollagen III N-terminal peptide [NT-procollagen III], galectin 3, C-telopeptide for type I collagen). Assays were performed at the HFN biomarker core laboratory (University of Vermont, Burlington, VT).16 Details of the RELAX CPXT protocol and HFN CPXT core laboratory (Massachusetts General Hospital, Boston, MA) methodologies have been reported.12

Briefly, symptom-limited CPXT with simultaneous expired ventilatory gas analysis was performed on a treadmill or bicycle ergometer. Percent-predicted peak VO2 was calculated according to published age and sex-normalized values.11 Age, sex, body weight, and mode-specific predicted peak VO2 was also calculated using the Wasserman equation.14,15 Entry criteria specified maximal effort as evidenced by a peak respiratory exchange ratio>1.0. The ventilatory anaerobic threshold was determined by the V-slope method.16 Peak oxygen pulse, reflecting oxygen consumption per heart beat during exercise, was obtained from the ratio of peak VO2 to peak exercise HR. Peak circulatory power was defined as the product of peak VO2 and peak systolic blood pressure, while circulatory stroke work was derived from the ratio of circulatory power to peak exercise HR.17 The VO2/VCO2 slope for the entire duration of exercise was calculated based on 10 s averaged V̇O2 (L/min) and V̇CO2 (L/min) data.18

Resting HR was documented after 5 minutes in a stationary position before CPXT. Peak HR was defined as HR at peak VO2. Chronotropic response was expressed as the change in HR from rest to peak exercise. Age-predicted maximal HR was defined with the Astrand (220-age),19 and Brawner (164−[0.7×age]) formulae, and each used to calculate a chronotropic index (CI) reflecting the percentage of HR reserve used (change in HR from rest to peak exercise/age-predicted maximal HR minus resting HR). Clinically significant chronotropic incompetence was defined as a CI <0.8 for patients not taking β-blockers and <0.62 in patients reporting active β-blocker use (Astrand formula). No β-blocker correction was used for chronotropic incompetence defined by the Brawner formula. HR recovery was taken as the absolute difference in HR between peak exercise and at 1 minute during exercise unloading or cessation. A HR recovery ≤18 bpm was considered abnormal.20

Statistical Analysis
Continuous data are presented as mean±SD or median (25th–75th percentiles) as appropriate; categorical data are presented as frequency (%) within each group (AF versus SR). Baseline characteristics and CPXT parameters for the RELAX study population stratified by rhythm status were compared using the t test or Wilcoxon rank-sum test for continuous variables, and χ2 test for categorical variables. Univariable and multivariable linear regression analyses for prespecified pertinent variables were performed to define the association between rhythm status and peak VO2. To adjust for the pathophysiological role of chronotropic response to exercise, a linear regression model was used to examine the relationship between CI and peak VO2 or peak workload with an interaction term included for rhythm status, thereby comparing the slope of the VO2–CI or workload–CI relationship between patients in AF and SR. Normality of model residuals was tested using the Kolmogorov–Smirnov test and visually assessed for symmetry. Analyses were performed using SAS version 9.2; P<0.05 (2-sided) was considered statistically significant.

Results
Patient Characteristics
RELAX enrolled 216 patients with HFpEF (mean age, 69±10 years; 48% women) of whom 79 (37%) had AF, 124 (57%) were in SR, and 13 (6%) were in other rhythms (excluded from this analysis). Patients in AF were older than those in SR, but had similar reported symptom severity (New York Heart Association class, Minnesota living with heart failure questionnaire total score), distribution of comorbidities, hemoglobin, and renal function (Table 1). Loop diuretic and digoxin therapy were more frequent, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use was less frequent, and β-blocker use was similar among patients in AF when compared with those in SR.

LV dimensions and LV mass index were comparable between AF and SR; however, AF was associated with worse systolic function at rest (lower LVEF, stroke volume, endocardial, and midwall fractional shortening). Although E/e' was similar between groups, other parameters of LV diastolic function were significantly worse in AF (shorter deceleration time, higher right atrial pressure, and larger left atrial volume index). Pulmonary artery systolic pressures were also higher in AF. Neurohumoral activation was more severe in AF relative to SR (elevated plasma N-terminal pro-B-type natriuretic peptide, aldosterone, and endothelin-1; Figure 1). Troponin I levels were higher in AF than in SR, consistent with greater myocardial necrosis (Figure 1). Plasma markers of fibrosis (NT-procollagen III, C-telopeptide for type I collagen, and galectin 3) were higher in AF than in SR; however, only C-telopeptide for type I collagen reached statistical significance (Table 1).

Exercise Performance
Fewer patients in AF performed bicycle ergometry (52% AF versus 68% SR; P=0.02). Both groups performed a maximal
Table 1. Baseline Characteristics by Rhythm Status at Enrollment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atrial Fibrillation (n=79)</th>
<th>Sinus Rhythm (n=124)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72.7±9.17</td>
<td>65.7±10.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>32 (41)</td>
<td>67 (54)</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.2±6.4</td>
<td>34.7±8.2</td>
<td>0.14</td>
</tr>
<tr>
<td>Rest systolic BP, mmHg</td>
<td>126±15</td>
<td>129±18</td>
<td>0.17</td>
</tr>
<tr>
<td>Rest diastolic BP, mmHg</td>
<td>71±10</td>
<td>69±10</td>
<td>0.18</td>
</tr>
<tr>
<td>Rest HR, bpm</td>
<td>72±13</td>
<td>68±11</td>
<td>0.04</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>42 (53)</td>
<td>65 (52)</td>
<td>0.92</td>
</tr>
<tr>
<td>MLWHFQ score</td>
<td>46±21</td>
<td>45±24</td>
<td>0.70</td>
</tr>
<tr>
<td>Galectin 3, ng/mL</td>
<td>14.3 (11.7–19.7)</td>
<td>13.6 (10.8–16.9)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cystatin C, mg/L</td>
<td>1.4 (1.1–1.7)</td>
<td>1.3 (1.0–1.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hb, mg/dL</td>
<td>12.6 (12.1–13.8)</td>
<td>13.0 (11.9–13.9)</td>
<td>0.58</td>
</tr>
<tr>
<td>NT-procollagen III, μg/L</td>
<td>8.1 (6.4–10.7)</td>
<td>7.5 (5.5–9.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>CITP, μg/L</td>
<td>6.7 (5.5–10.2)</td>
<td>5.7 (4.2–9.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Galectin 3, ng/mL</td>
<td>14.3 (11.7–19.7)</td>
<td>13.6 (10.8–16.9)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Comorbidities
- Hypertension: 65 (82) vs 108 (87); 0.35
- Diabetes mellitus: 28 (35) vs 56 (45); 0.17
- COPD: 15 (19) vs 24 (19); 0.95
- History of AF: 79 (100) vs 28 (23); <0.0001
- GFR, mL/min per 1.73 m²: 65.3 (51.6–77.2) vs 65.6 (43.5–86.0); 0.77
- Cystatin C, mg/L: 1.4 (1.1–1.7) vs 1.3 (1.0–1.7); 0.07
- Hb, mg/dL: 12.6 (12.1–13.8) vs 13.0 (11.9–13.9); 0.58
- NT-procollagen III, μg/L: 8.1 (6.4–10.7) vs 7.5 (5.5–9.5); 0.10
- CITP, μg/L: 6.7 (5.5–10.2) vs 5.7 (4.2–9.0); 0.003
- Galectin 3, ng/mL: 14.3 (11.7–19.7) vs 13.6 (10.8–16.9); 0.15

Medication at enrollment
- ACEI/ARB: 49 (62) vs 97 (78); 0.01
- β-blocker: 63 (80) vs 91 (73); 0.30
- Aldosterone antagonist: 10 (13) vs 11 (9); 0.39
- Loop diuretic: 77 (98) vs 78 (63); <0.0001
- Digoxin: 18 (23) vs 3 (2); <0.0001
- Calcium channel blocker: 28 (35) vs 36 (29); 0.34
- Amiodarone: 1 (1) vs 7 (6); 0.15
- Other antiarrhythmic: 3 (4) vs 6 (5); 1.00
- Aspirin/thienopyridine: 31 (39) vs 90 (73); <0.0001
- Warfarin: 69 (87) vs 22 (18); <0.0001

Echocardiography
- LVEF, %: 59±8 vs 63±7; 0.002
- Rest cardiac index, L/min per m²: 2.4±0.6 vs 2.6±0.7; 0.04
- Stroke volume, mL: 70±20 vs 84±24; 0.0001
- eFS, %: 36±7 vs 40±6; 0.0002
- mFS, %: 19±4 vs 21±3; 0.0009
- LV mass index, g/m²: 84±33 vs 82±33; 0.77
- LV diastolic dimension, cm: 4.6±0.7 vs 4.7±0.6; 0.71
- Deceleration time, ms: 172±48 vs 203±44; <0.0001
- LAVI, mL/m²: 62±25 vs 41±13; <0.0001
- PASP, mmHg: 45±12 vs 41±12; 0.045

(Continued)
Although a majority of patients with HFpEF had abnormal HR recovery consistent with autonomic dysfunction, the severity of impaired HR recovery was similar between groups.

Discussion
This analysis of the RELAX HFpEF cohort demonstrates that important phenotypic differences exist between HFpEF patients with and without AF and is the first comprehensive analysis of the impact of AF on exercise capacity in HFpEF. Consistent with our hypothesis, HFpEF patients in AF were older and exhibited worse LV systolic and diastolic function at rest, more severe neurohumoral activation, and greater impairment of exercise capacity compared with HFpEF patients in SR. Peak VO₂ was lower in AF, despite adjustment for pertinent variables, and was not accompanied by a higher chronotropic response as has been seen in patients with HFrEF and AF. Ventilatory efficiency was lower (steeper $V_e/V_{CO₂}$ relationship) in AF, suggesting greater impairment of pulmonary perfusion during exercise. Peak exercise systolic blood pressure, circulatory power, and circulatory stroke work were lower and peak $O_2$ pulse tended to be lower in AF, suggesting impaired systolic reserve function. These findings demonstrate that mechanisms beyond altered chronotropic response mediate the more impaired exercise tolerance in patients with HFpEF and AF and suggest that AF is a marker of a more advanced HFpEF phenotype.

In patients with HFrEF, AF is associated with more severe symptoms and LV systolic impairment. In HFrEF, a rhythm control strategy does not result in better outcomes than rate control, and β-blockers may have reduced pharmacological efficacy contrary to established benefits for patients in SR.

Importantly, characteristics associated with AF in HFpEF are less well documented, despite the high prevalence of AF in HFpEF and evidence of equivalent or perhaps stronger association with morbidity and mortality in HFpEF than in HFrEF. Existing studies are highly discrepant, have limited phenotypic characterization, and enrolled patients during a hospitalization for HF which may not accurately reflect the HFpEF population at large. Although the CHARM-Preserved trial studied stable HFpEF outpatients with and without AF, the prevalence of coronary artery disease was higher than typically observed in HFpEF, and HFpEF was defined by a LVEF >40%, thereby including patients with potential HFrEF pathophysiology.

RELAX enrolled stable patients with chronic HFpEF in SR and AF, ≥3 months out from any HF hospitalization, exhibiting a LVEF ≥50% consistent with current diagnostic criteria. In this setting, AF was associated with older age and worse LV systolic and diastolic function, mirroring observations in HFrEF but contrary to sparse available data in HFpEF and AF, where systolic function (LVEF) has been reported as similar to SR. Furthermore, in contrast to the findings of Linssen et al. and perhaps because of the exclusion of patients with LVEF 40%–49%, we found N-terminal pro-B-type natriuretic peptide to be significantly elevated in AF relative to patients with HFpEF-SR. This corroborates baseline findings in the I-Preserve population and may pertain to AF or more severe HF in patients with HFpEF-AF. More severe HF is also suggested by elevation in other heretofore unstudied biomarkers of HF severity in patients with HFpEF-AF (aldosterone, endothelin-1, and troponin I), greater diuretic use, and a lower cardiac index. A higher resting $V_{O₂}$ was observed in AF which,
therapy addressing the atrial substrate in patients with HF and AF, which is currently under investigation.33

AF has been associated with reduced functional capacity in HFrEF22 and in patients without structural heart disease34; however, prior studies of exercise tolerance in HFrEF have mostly excluded patients with AF.23,35,36 Similarly, HFrEF has been under-represented in AF intervention trials,12,24,37 thus the impact of AF on exercise capacity and cardiopulmonary function during exercise in HFrEF remains unclear. Fung et al25 reported the mean 6MWD to be lower in hospitalized HFpEF patients with AF (279±66 m; n=42) when compared with patients in SR (338±86 m; n=104); however, formal cardiopulmonary stress testing was not performed. In the present analysis, we confirm and extend this observation in several respects.

Our novel principal finding is that, compared with SR, HFpEF patients with AF have a lower peak VO2 both in absolute terms and relative to age, sex, body-size, and exercise mode–adjusted predicted values. Furthermore, we demonstrate that the impaired exercise capacity in AF is not explained by differences in resting LVEF or altered chronotropic response, suggesting a specific effect of AF on cardiac reserve. Rhythm irregularity38 and loss of atrial contribution to LV filling 39 are recognized to impair cardiac output in AF. Indeed, the lower circulatory work, mm Hg·mL/kg per min 15.5±5.7 19.4±9.1 <0.0001
Chronotropic indices
Rest HR (pre-exercise) 72±12 68±14 0.14
Peak HR, bpm 109±27 111±24 0.69
Chronotropic response, bpm 37±23 42±20 0.17
Age-predicted maximal HR, bpm Astrand formula* 147±9 154±10 <0.0001
Brawner formula† 113±6 118±7 <0.0001
Chronotropic index Astrand formula* 0.51±0.34 0.50±0.25 0.73
Brawner formula† 1.10±1.08 0.92±0.61 0.19
HRR, bpm 11±15 10±9 0.51
HRR≤18 bpm, n (%) 55 (73) 94 (83) 0.14

6MWD indicates 6 minute walk distance; DBP, diastolic blood pressure; HR, heart rate; HRR, absolute heart rate recovery at 1 min post exercise; RER, respiratory exchange ratio; SBP, systolic blood pressure; VAT, ventilatory anaerobic threshold; VO2peak, carbon dioxide output; VE, minute ventilation; VE/VO2peak, slope of the relationship between minute ventilation and carbon dioxide output; and VO2peak, oxygen consumption.

Continuous variables are shown as mean±SD; categorical variables are shown as count (percentage).

*220–age.19
†164−[0.7×age].20

as in HFrEF, may signify increased resting energy demands or hypermetabolism corresponding to increased HF severity.31,32 These findings support the rationale for aggressive upstream
which may contribute to earlier exercise cessation and reduced functional capacity in AF. An increased \( V_E/VCO_2 \) slope has been observed in patients with permanent AF compared with control subjects in SR\(^{34,44} \). However, Ariansen et al.\(^{43} \) reported no difference in ventilatory efficiency between AF and SR when patients with HF were excluded from their analysis. Further, Agostoni et al.\(^{22} \) did not observe an association between AF and \( V_E/VCO_2 \) slope in chronic HFrEF. Therefore, it remains unclear whether the steeper \( V_E/VCO_2 \) slope can be ascribed to a specific effect of AF on exercise hemodynamics. More likely, AF is a marker of reduced pulmonary vascular reserve, as well as more impaired diastolic reserve function in patients with HFpEF, as suggested by the differences in baseline characteristics.

Interestingly, HFpEF patients with AF did not display an exaggerated chronotropic response to exercise compared with patients in SR, contrary to previous findings in lone AF.\(^{34,44} \) Peak HR and CI were similar between AF and SR, whereas peak \( V_O_2 \) and workload were lower in patients with AF; however, the relationships between CI and peak \( V_O_2 \) or workload were not significantly different for AF than for SR. Chronotropic incompetence is a common feature in HFpEF patients in SR,\(^2 \) and our data demonstrate that HFpEF patients with AF have a similar prevalence of chronotropic incompetence when their prevalence of beta-blocker use is equivalent to SR. Notably, no symptomatic or prognostic benefit has been demonstrated with strict versus lenient HR control in the general AF population\(^{45} \) including a post hoc analysis of patients with HF\(^{46} \), although the latter did not examine the impact of rate control strategy on events stratified by HFpEF and HFrEF. Therefore, although current American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend HR control in HFpEF patients with AF (class IC),\(^{47} \) the optimal level of HR control in HFpEF, particularly with respect to exercise capacity, has yet to be established.

**Study Limitations**

Rhythm was classified by the presence or absence of AF on enrollment electrocardiography. Consequently, HFpEF patients with previous or paroxysmal AF may have been classified as SR although this would likely serve to underestimate the observed differences. Greater frequency of treadmill exercise versus bicycle ergometry in AF would also minimize any differences in peak \( V_O_2 \) from SR as bicycle ergometry is generally associated with a lower peak \( V_O_2 \). Information on right heart structure and function along with duration of AF and decisions on rate or rhythm control were unavailable although antiarrhythmic agents were used in <10% of the overall population. Therefore, these data pertain to patients with and without persistent AF in the context of heterogeneous AF and HF therapeutic strategies.

**Conclusions**

In patients with HFpEF, AF is associated with important phenotypic and functional differences: older age, impaired LV systolic and diastolic function and functional reserve, more severe neurohumoral activation, and impaired exercise tolerance, supporting AF as a marker of more advanced HF phenotype in HFpEF. Furthermore, in the context of \( \beta \)-blocker
therapy, chronotropic incompetence is equally common in HFrEF patients in AF or SR. Further study is required to determine whether different rate control strategies or indeed, rhythm control in patients with HFrEF and AF may favorably affect exercise tolerance.

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Disclosures
None.

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Exercise Capacity in HFpEF (RELAX) trial enrolled 216 ambulatory patients who met rigorous entry criteria for HFpEF and cardiac limitation to exercise. The aim of this study was to determine clinical, biochemical, and echocardiographic characteristics associated with exercise intolerance in patients with HFpEF. The study found that patients with HFpEF and AF were older, had worse left ventricular systolic and diastolic function at rest, more severe neurohumoral activation, and greater impairment of exercise capacity. Ventilatory efficiency and systemic reserve function were also lower in HFpEF patients with AF. Moreover, the study demonstrated that the lower exercise capacity in AF was not explained by differences in age, sex, resting left ventricular function, or altered chronotropic response, suggesting a specific effect of AF on cardiac reserve. These data serve to underscore the significance of AF in patients with HFpEF and may be able to examine whether different therapeutic strategies, including rate or rhythm control, may favorably affect exercise tolerance in this setting.
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