Enhanced ventricular-arterial coupling during a 2-year physical activity programme in patients with rheumatoid arthritis: a prospective substudy of the physical activity in rheumatoid arthritis 2010 trial

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Objective. To establish how guided physical activity in patients with rheumatoid arthritis (RA) without known cardiovascular disease affected vascular and cardiac function, and how these two entities were prospectively interconnected in this patient group.

Methods. Prospective substudy of 29 participants in the Physical Activity in RA (PARA) 2010 trial. All subjects were examined at baseline, at year 1 and 2 with measures of pulse wave velocity and arterial augmentation index, as well as echocardiographic evaluation of diastolic parameters and ventricular-arterial coupling. Muscle strength and aerobic exercise capacity were assessed at baseline and yearly. All participants performed physiotherapist-guided aerobic and muscle strength exercise during 2 years and were reminded through SMS to report physical activity progress.

Results. This cohort of patients with RA exhibited increased vascular stiffness despite normal blood pressure. At baseline, lower muscle strength was associated with increased vascular stiffness (β = 0.68; P = 0.004), whereas lower aerobic working capacity was associated with left ventricular diastolic dysfunction (β = 0.85; P = 0.03). There was a significant positive correlation between vascular stiffness and diastolic dysfunction at baseline (R2 = 0.64) and for the changes in those parameters observed during 2 years of guided physical activity. Finally, a significant improvement in ventricular-arterial coupling was observed after exercise (P < 0.001).

Conclusion. These results indicate that although differentially associated with physical capacity parameters, improved vascular stiffness and improved diastolic dysfunction are interrelated, and that an optimization of the ventricular-arterial coupling may contribute to the beneficial effects of physical activity in patients with RA.

Keywords: augmentation index, echocardiography, inflammation, pulse wave velocity.

Introduction

Patients with rheumatoid arthritis (RA), psoriasis, systemic lupus erythematosus, multiple sclerosis and several other autoimmune diseases display a significantly increased risk for cardiovascular events [1]. For example, the relative risk of developing myocardial infarction is twice as high in patients with RA as compared with the general population [2]. The incidence of cardiovascular events is not elevated until after the onset of RA and then rises significantly within 2 years [3]. A
rheumato-cardiovascular comorbidity may hence exist, which is not due to shared risk genes or risk factors, but potentially caused by an increased inflammation also in blood vessels of patients with RA [1]. The latter notion has also received support from recent findings that the disease duration is an independent predictor of vascular stiffness in patients with RA without known cardiovascular comorbidities [4]. Arterial stiffness measured as pulse wave velocity (PWV) is an established surrogate marker for cardiovascular risk, vascular adaptation and a valuable tool for assessing subclinical CVD in for example patients with RA [5].

In addition to the above-mentioned vascular changes and an increased risk of ischaemic events, patients with RA also exhibit myocardial changes in terms of diastolic dysfunction [6, 7] and the development of heart failure (HF) [8], even in the absence of ischaemic events [9]. The dominant type of HF in RA is characterized by preserved ejection fraction (HFpEF) and diastolic dysfunction [8]. In early RA, patients have increased levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) as compared with control groups, which correlate with disease activity score (DAS) and clinical disease activity index [10], further strengthening the association of RA disease activity with cardiovascular changes.

Although it is well established that arterial stiffness has a strong connection with HF [11, 12], the interaction between these two factors has not previously been studied in RA. The Swedish prospective PARA (Physical Activity in Rheumatoid Arthritis) study established that coaching patients with early RA to healthy physical activity improved perceived health status and muscle strength [13]. A follow-up study, PARA 2010, aimed to determine if increased physical activity and exercise improves perceived health, reduces pain and fatigue, increases muscle function and aerobic capacity, impacts psychosocial factors and prevents future cardiovascular events in patients with RA [14]. In this report, we present the results of a PARA 2010 substudy, which was initiated with the aim to establish if coached physical activity in patients with RA without known CVD improved vascular and diastolic function, as assessed by repeated examinations of PWV and arterial augmentation index (Aix), as well as echocardiographic evaluation of diastolic function and ventricular-arterial coupling.

### Methods

#### Study population

This is a substudy of the prospective PARA 2010 study (Trial registration number: ISRCTN25539102) [14]. For the present substudy, 29 PARA 2010 participants were included. At baseline, 69% were taking biological RA medications, 55% other disease-modifying anti-rheumatics (DMARD), 31% used NSAIDs and 17% were using cortisone. Inclusion criteria were RA according to American College of Rheumatology, without a history of CVD, without known depressed systolic function and without atrial fibrillation. During the collection of baseline data, normal left ventricular systolic function was confirmed by echocardiography in all participants. No subject exhibited suspicion of exercise-induced myocardial ischaemia on an exercise bicycle test with ECG and blood pressure monitoring.

The study protocol was approved by the Stockholm regional ethics committee (reference number 2012/769-32), and those willing to participate were given an opportunity to receive additional information about the trial through telephone calls before accepting to participate.

#### Physical activity support programme

The physical activity support programme has been described in detail in previous reports from PARA 2010 [15, 16]. In brief, participants were encouraged to perform moderate-intensity physical activity for 30 min on most days of the week for 1 year. They were provided with pedometers and received instructions on how to use it as well as a web page for activity monitoring. In addition, the cohort was encouraged to take part in at least two weekly 45-min circuit training sessions that combined aerobic and muscle strengthening exercises. Participants received weekly short text message (SMS) reminders and responded to the study coordinator whether they fulfilled the physical activity according to the programme. During the second year, no physical activity guidance was performed, but participants were expected to continue the programme and report adherence in text messages.

#### Biomarkers

Blood samples were obtained at each visit (baseline, year 1, year 2). Plasma high-sensitivity C-reactive protein (hs-CRP) concentrations were...
measured by a particle-enhanced immunoturbidimetric method (Roche) with a measure interval of 0.1–20 mg mL⁻¹. Erythrocyte sedimentation rate (ESR) was measured using the Westergren method.

Echocardiography

Echocardiography examinations were performed by two experienced operators using a Vivid E9 (GE Healthcare, Milwaukee, WI, USA). Echocardiographic images were digitally stored for offline analysis using commercially available software (EchoPAC PC version 110.0.0, GE Healthcare). Each patient was evaluated using a standard two-dimensional pulsed and continuous wave Doppler, and measurements were taken according to established guidelines. All examinations were analyzed in a blinded fashion by an experienced reader.

Standard left ventricular (LV) systolic and diastolic dimensions were measured. The diastolic transmural flow velocities (E- and A-wave) were recorded using pulsed wave Doppler at the mitral leaflet tips in the apical four chamber view. e’ was measured by tissue Doppler at the septal and lateral mitral annulus, and the mean of the two measures was used. Stroke volume (SV) was calculated by multiplying the cross-sectional area of LV outflow tract (LVOT) with the Doppler-derived velocity time integral (VTI_LVOT).

Effective arterial and ventricular elastance measurements

Effective arterial elastance (Ea), which constitutes an overall index of LV afterload in the time-domain, was calculated as \( \text{Ea} = \frac{\text{LVESP}}{\text{SV}} \); where LVESP is the LV end-systolic pressure estimated from the equation: \( \text{LVESP} = 0.9 \times \text{SBP} \), where SBP is the systolic systemic blood pressure [17].

LV end-systolic elastance (Ees) was calculated using the single-beat approach developed by Chen et al.: \( \text{Ees} = \frac{\text{LVEDP} - (\text{EN}_{d(\text{est})} \times \text{LVESP})}{[\text{SV} \times \text{EN}_{d(\text{est})}]} \) [18]. For this equation, LV end-diastolic pressure (LVEDP) was estimated as: \( \text{LVEDP} = 11.96 + 0.596 \times \frac{\text{E}}{e'} \), as previously described [19]. \( \text{EN}_{d(\text{est})} \) represents the estimated normalized ventricular elastance at arterial end-diastole and was calculated as the group-averaged normalized Ees values [18] by the equation: \( \text{EN}_{d(\text{est})} = 0.0275 - 0.165 \times \text{EF} + 0.3656 \times \frac{\text{DBP}}{\text{SBP}} + 0.515 \times \text{EN}_{d(\text{avg})} \), in which EF is the ejection fraction and \( \text{EN}_{d(\text{avg})} \) is given by the following seven-term polynomial function:

\[
E_{\text{ND(avg)}} = \sum_{i=0}^{7} a_i \times t_i^{\text{ND}}
\]

where summation is performed for \( i = 0 \sim 7 \), using values for \( a_i \) of (0.35695; -7.2266; 74.249; -307.39; 684.54; -856.92; 571.95; -159.1) [18]. The \( t_{\text{ND}} \) is the ratio of the pre-ejection (R-wave to flow-onset) to the total systolic period (R-wave to flow-termination), with the time at onset and termination, respectively, of flow obtained from pulsed wave Doppler curve in LVOT [18].

The ventricular-arterial coupling was calculated as the \( \text{Ea}/\text{Ees} \) ratio [20] to evaluate the interaction between cardiac performance and vascular function.

Blood pressure and arterial stiffness

Supine blood pressure was measured using a manual sphygmomanometer after 5 min of rest.

Pulse wave velocity and augmentation index (Aix) were measured at a constant room temperature and calculated using the oscillometric Arteriograph (TensioMed, Budapest, Hungary). The readings were achieved through recording oscillations with a special high-fidelity sensor when the cuff pressure exceeded systolic blood pressure by 35–40 mmHg [21]. This technique is possible to utilize because a pulse wave (also referred to as ‘early systolic peak’) is created after myocardial contraction. When the pulse propagates further, it reaches the aortic bifurcation which generates a second wave which is referred to as the ‘late systolic peak’. Blood pressure measurements obtained with the Arteriograph corresponded to those obtained in manual measures and were used for calculations of the mean arterial blood pressure (MAP) according to the formula: \( \frac{\text{MAP}}{3} = \frac{\text{SBP} + 2 \times \text{DBP}}{3} \).

Clinical assessment

The DAS28 (0–10 scale) is based on the erythrocyte sedimentation rate (mm h⁻¹), the number of swollen (n = 28) and tender (n = 28) joints, and the patient’s self-reported general health perception (VAS, 0–10).

Physical testing

All assessments used in the study were performed according to the PARA 2010 study protocol as...
previously described [14, 16]. During measurements of all physical performance variables, the same test equipment was used at each clinic to ensure that the patients were evaluated in a standardized setting both at baseline and at each follow-up.

Two tests of muscle function were performed; Grippit, which uses an electronic dynamometer device for measuring maximum grip strength in Newton and the Timed-Stands Test (TST), which assesses lower extremity function. TST quantifies the time in seconds required for ten full stands from a sitting position in an armless chair.

A maximal exercise stress test was also performed on another occasion to rule out cardiac ischaemia and assess cardiorespiratory functional capacity with continuous ECG and blood pressure monitoring. A starting load of 50 W was used with a 20 W min \(^{-1}\) increase in intensity, and the results were expressed as either W or as percent of predicted.

Statistical analysis

Data are expressed as median and 95% confidence intervals. To determine statistically significant changes during the 2-year study protocol, an ANOVA on ranks analysis was used. The median values of PVW were age stratified per decades to allow comparisons with previously reported reference values in the general population [22]. Multiple regression models were created to determine correlations between diastolic and vascular parameters at baseline when adjusting for age, gender, BMI, resting heart rate and MAP. To examine what determined changes in these cardiovascular parameters during the study period (and adjust for confounding), multiple regression analyses were performed using the delta values of parameters after 2 years of exercise to determine if patients who improved their vascular parameters also enhanced their diastolic parameters adjusting for the same confounders as in the baseline analyses.

All statistical tests were two-sided, and \( P < 0.05 \) was considered statistically significant. The statistical analyses were performed using SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Table 1 displays the investigated parameters at baseline, and at each yearly follow-up. A statistically significant increase in E/A ratio was observed over the entire study period and a trend towards decreased PWV and Aix at Year 1. For the physical performance measures, a significant improvement in TST was observed, and a trend towards improved maximal exercise capacity as per cent of predicted Watts was observed, and were not significantly altered during the study period (Table 1).

Comparing the median PWV values in each age category in this study with the previously reported normal values in a general population [22] showed a statistically significantly higher PWV in the two middle age groups at baseline (Fig. 1a), which persisted at Year 2 (Fig. 1b).

We next sought to determine the relation between diastolic cardiac function and vascular stiffness at baseline, and their respective relation to physical exercise capacity. A multivariable analysis of the baseline characteristics was performed after adjustment for age, gender, BMI, heart rate and MAP, which are all established confounders for vascular stiffness measures and diastolic function [23–28]. Of the physical parameters measured, TST was significantly associated with PWV, and there was a trend association for muscle strength measured by grippit with Aix and PWV (Table 2). Of the echocardiographic measures, the E/A ratio was significantly and positively associated with the maximal exercise capacity expressed as either Watts or per cent of predicted Watts (Table 2). Finally, hs-CRP was significantly associated with Aix in this analysis (Table 2).

The results of the multivariable analysis examining the relation between vascular stiffness and diastolic function are shown in Table 3. Those analyses revealed a statistically significant inverse correlation for \( e' \) with Aix and PVW, and for the E/A ratio with Aix (Table 2). There was, in addition, a trend towards a positive correlation of the vascular indices with DecT, albeit not reaching statistical significance.

Given the significant association between \( e' \) with Aix and PWV at baseline, we subsequently assessed the changes in cardiovascular properties between the start of the trial and the second year. In a multivariable analysis, a statistically
significant inverse correlation was found between the change in Aix and e’ (β-coefficient = −0.75; \( P = 0.002 \)). The same analysis for the change in PWV revealed a similar association (β-coefficient = −0.70; \( P = 0.03 \)).

As these analyses indicated an interconnection between changes in vascular and ventricular function, we finally assessed the ventricular-arterial coupling by means of echocardiographic measures. Whereas the changes in \( E_a \) were not statistically significant (Fig. 2a), there was a significant increase in \( E_{es} \) (Fig. 2b). The resulting significant decrease in the \( E_a/E_{es} \) ratio as a measure of enhanced ventricular-arterial coupling is shown in Figure 2c.
Fig. 1 Pulse wave velocity (PWV) in relation to reference values during 2-year physical exercise in patients with RA. (a) Baseline, (b) Year 2.

Table 2 Correlation of diastolic and vascular parameters with physical capacity at baseline after adjustment for age, gender, BMI, heart rate and mean arterial blood pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>E/A</th>
<th>c' (m s(^{-1}))</th>
<th>Aix (%)</th>
<th>PWV (m s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grip power average Rt (N)</td>
<td>(\beta = 0.57)</td>
<td>(\beta = 0.04)</td>
<td>(\beta = -0.63)</td>
<td>(\beta = -0.50)</td>
</tr>
<tr>
<td></td>
<td>(P = 0.07)</td>
<td>(P = 0.92)</td>
<td>(P = 0.10)</td>
<td>(P = 0.18)</td>
</tr>
<tr>
<td>TST (s)</td>
<td>(\beta = -0.29)</td>
<td>(\beta = -0.19)</td>
<td>(\beta = 0.32)</td>
<td>(\beta = 0.68)</td>
</tr>
<tr>
<td></td>
<td>(P = 0.24)</td>
<td>(P = 0.45)</td>
<td>(P = 0.19)</td>
<td>(P = 0.004)</td>
</tr>
<tr>
<td>Exercise test max exertion (W)</td>
<td>(\beta = 0.85)</td>
<td>(\beta = 0.10)</td>
<td>(\beta = -0.333)</td>
<td>(\beta = -0.468)</td>
</tr>
<tr>
<td></td>
<td>(P = 0.03)</td>
<td>(P = 0.81)</td>
<td>(P = 0.418)</td>
<td>(P = 0.280)</td>
</tr>
<tr>
<td>Exercise test % of expected</td>
<td>(\beta = 0.638)</td>
<td>(\beta = 0.11)</td>
<td>(\beta = 0.05)</td>
<td>(\beta = -0.37)</td>
</tr>
<tr>
<td></td>
<td>(P = 0.040)</td>
<td>(P = 0.74)</td>
<td>(P = 0.87)</td>
<td>(P = 0.20)</td>
</tr>
<tr>
<td>hs-CRP (mg L(^{-1}))</td>
<td>(\beta = -0.55)</td>
<td>(\beta = -0.48)</td>
<td>(\beta = 0.68)</td>
<td>(\beta = 0.49)</td>
</tr>
<tr>
<td></td>
<td>(P = 0.07)</td>
<td>(P = 0.12)</td>
<td>(P = 0.02)</td>
<td>(P = 0.07)</td>
</tr>
</tbody>
</table>

E/A Ratio, Ratio between early mitral inflow velocity and atrial systolic mitral velocity; c', Early diastolic mitral annular velocity; Aix aortic, Aortic augmentation index; PWV, Pulse Wave Velocity; hs-CRP, high-sensitivity C-reactive protein. Bold font style indicates a statistically significant relationship between column and row parameters.

Table 3 Multivariate analysis of vascular and diastolic function at baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>c' (m s(^{-1}))</th>
<th>E/A</th>
<th>DecT (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aix (%)</td>
<td>(\beta = -0.57)</td>
<td>(\beta = -0.54)</td>
<td>(\beta = 0.49)</td>
</tr>
<tr>
<td></td>
<td>(P = 0.01)</td>
<td>(P = 0.03)</td>
<td>(P = 0.10)</td>
</tr>
<tr>
<td></td>
<td>(R^2 = 0.68)</td>
<td>(R^2 = 0.61)</td>
<td>(R^2 = 0.31)</td>
</tr>
<tr>
<td></td>
<td>(\text{Adj } R^2 = 0.55)</td>
<td>(\text{Adj } R^2 = 0.45)</td>
<td>(\text{Adj } R^2 = 0.04)</td>
</tr>
<tr>
<td>PWV (m s(^{-1}))</td>
<td>(\beta = -0.47)</td>
<td>(\beta = -0.31)</td>
<td>(\beta = 0.44)</td>
</tr>
<tr>
<td></td>
<td>(P = 0.03)</td>
<td>(P = 0.18)</td>
<td>(P = 0.12)</td>
</tr>
<tr>
<td></td>
<td>(R^2 = 0.64)</td>
<td>(R^2 = 0.51)</td>
<td>(R^2 = 0.30)</td>
</tr>
<tr>
<td></td>
<td>(\text{Adj } R^2 = 0.49)</td>
<td>(\text{Adj } R^2 = 0.31)</td>
<td>(\text{Adj } R^2 = 0.22)</td>
</tr>
</tbody>
</table>

c', Early diastolic mitral annular velocity; E/A Ratio, Ratio between early mitral inflow velocity and atrial systolic mitral velocity; DecT, Deceleration time of the early mitral inflow velocity; Aix aortic, Aortic augmentation index; PWV, Pulse Wave Velocity. Bold font style indicates a statistically significant relationship between column and row parameters.
Discussion

Three major observations emerge from the present study. First, we confirm that patients with RA and without prevalent CVD exhibited increased vascular stiffness despite normal blood pressure. Second, we show that muscle strength and aerobic working capacity were associated with vascular stiffness and diastolic function, respectively, and that increased vascular stiffness measures were significantly associated with indices of diastolic dysfunction. Third, 2 years’ supported physical activity improved the ventricular-arterial coupling. Taken together, these results indicate that improved arterial and cardiac function over time are interconnected, and may contribute to the beneficial effects of physical activity in patients with RA [13, 15] even in individuals without apparent CVD.

Previous studies have established that patients with RA exhibit an increased vascular stiffness, measured as either Aix [29] or PWV [30], even in the absence of other CV risk factors. The present study confirms those findings and extends the observations by showing that lower extremity muscle function, as assessed by TST, significantly predicted PWV in this RA population, with a trend also for maximum hand grip strength as predictors for vascular stiffness. Loss of muscular tissue, referred to as sarcopenia, and increased arterial stiffness may both reflect a premature ageing in patients with RA [31].

There are conflicting results from previous studies that investigated connections between diastolic dysfunction and RA. While some trials concluded that there are correlations between left ventricular diastolic dysfunction and RA, other trials reported no significant correlations regarding the two conditions [32–35]. The present RA population exhibited a median E/A ratio below one while the median e’ was within the normal range, suggesting a grade 1 diastolic dysfunction (impaired relaxation). Interestingly, the E/A ratio was significantly correlated with the aerobic exercise capacity, but not to muscle strength, suggesting that impaired myocardial relaxation may be associated with low aerobic potential in patients with RA, as has previously been described in other patient populations [36, 37].

A link between arterial stiffness and diastolic dysfunction has been previously described in
patients with grade I left ventricular diastolic dysfunction at the earliest stage of HF [38]. Hence, it has been recommended that vascular function assessments could be a valuable complement to a comprehensive clinical evaluation of these patients [38]. However, no trial has investigated if there is a connection between arterial stiffness and diastolic dysfunction in patients with RA. In the present study, Aix but not PWV was associated with E/A and e’. Wave intensity studies have previously investigated the connection between systolic heart failure and vascular stiffness by analyzing wave reflections and Aix [11]. In a trial performed by Curtis et al., cardiovascular parameters between 67 patients with heart failure were compared to a control group of 29 healthy subjects [11] and wave reflections were found to be significantly increased in patients with heart failure, whereas no significant differences in Aix were found [11].

The relation between systemic inflammation, measured for example as hs-CRP, and cardiovascular risk has been well established [1]. There is in addition evidence that systemic inflammation is an important factor in developing arterial stiffness [39, 40] and this notion is supported by the present study, which revealed a significant correlation between Aix and hs-crp in patients with RA after adjusting for cardiometabolic confounders.

Aerobic exercise has been reported to reduce arterial stiffness in young and healthy individuals [41]. In elderly subjects [42] and in those with cardiometabolic risk factors [41], the effects of exercise on vascular stiffness appear to be more dependent on blood pressure. The present study establishes improved diastolic but not vascular function in the whole population of patients with RA after controlled physical exercise, although the sample size was small. Nevertheless, we discovered that after adjustment for possible confounding, there was a strong and statistically significant association between changes in vascular and diastolic function. In addition to being significantly correlated at baseline, the significant associations between improvements in vascular stiffness and diastolic function during the 2-year exercise programme indicate that these two parameters are closely related to each other and may be part of the beneficial effects of improved muscle strength and increased aerobic exercise capacity in patients with RA.

To further explore this interconnection between vascular and cardiac function, we determined the ventricular-arterial coupling as the ratio between $E_a$ and $E_{es}$ calculated by means of echocardiographic measures. Ventricular-arterial coupling has been recognized as a key determinant of global cardiovascular performance [20]. The significant decrease in the $E_a/E_{es}$ ratio observed during the present study indicates that physical exercise induced an optimization of ventricular-arterial coupling, which hence in turn may contribute to beneficial cardiovascular functional modulation in patients with RA. The latter has received support from a previous investigation of ten healthy senes- tary seniors (>65 years) undergoing a 1 year of progressive exercise training which reported a significant decrease in left ventricular afterload despite no improvements in aortic stiffening [43].

Major strengths of this study include the prospective design with close monitoring of the participant’s adherence to the physical activity programme and the repeated assessments of vascular and cardiac phenotype as well as physical capacity in terms of both muscle strength and aerobic capacity. This has, to our knowledge, not been investigated previously in RA. This study also has some limitations, the most obvious one being the relatively small sample size. As patients were tasked to report themselves on how physically active they had been, the possibility of reporting bias should be acknowledged. The noninvasive echocardiographic estimations of ventricular-arterial coupling should also be considered as a limitation. Finally, although arteriography measures to determine vascular stiffness through PWV and Aix is reproducible and simple to perform [44], using state of the art measures, such as carotid-femoral pulse wave velocity in a larger cohort is warranted in this patient group.

In summary, the present study confirms an increased vascular stiffness in RA even in the absence of prevalent cardiovascular disease. In line with previous studies in other patient categories, supported physical activity did not improve vascular stiffness despite significant improvements in muscle strength and a trend towards improved aerobic capacity. Nevertheless, the present study raises the notion of an association of vascular stiffness with diastolic function in patients with RA, and suggests that an improved ventricular-arterial coupling may contribute to the beneficial
effects of exercise training in patients with RA even in the absence of prevalent CVD.

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Conflict of interest statement

None declared.

References


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