Supplementary Online Content

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Methods: Selection of Cases From a Perinatal Registry, Definitions, Cardiac Magnetic Resonance Acquisition and Analysis, and Incremental Exercise Testing Methodology

Study design

Ambispective cohort study including young adults (20-40 y old), 77 born with SGA and 81 with normal intrauterine growth (controls) identified from a perinatal cohort. Figure S1 presents the CONSORT flow diagram of the study population. Subjects were randomly identified (computer-generated random selection) within a perinatal registry of 32,490 deliveries taking place from 1975 to 1995 in a tertiary university hospital in Barcelona (Hospital Sant Joan de Déu), Spain. We first identified SGA cases randomly from the perinatal registry, and then one control for each case was randomly identified from registry from the same year and month of birth of the SGA case. From 532 adults initially contacted, 287 refused to participate and 87 were excluded due to current pregnancy (n=25), twin pregnancy (n=17), neonatal macrosomia (defined as birthweight above the 95th centile) (n=16), major mental disorder (n=11), congenital malformations (n=10), genetic syndromes (n=5) or professional sport practice (n=3), leading to a final sample size of 77 SGA and 81 controls. SGA was defined as a birth weight below the 10th centile for gestational age according to both contemporary[1] and current[2] local standards. SGA was defined as being below the 10th centile for both reference curves. Controls were defined as birth weight above 10th centile for the two standards used[1-2].

Young adults recruited for the study were evaluated with a medical history and physical examination, blood pressure, questionnaires for physical activity,[3] smoking[4] and glucose and lipid profile tests.

The level of physical activity ("fitness") prior to the exercise test was determined using a standardized questionnaire[3] and categorized into: high if vigorous activity on at least 3 days achieving a minimum total physical activity of at least 1500 metabolic equivalent of task (MET)-minutes/week, or five or more days of any combination of walking, or moderate or vigorous activities that achieve at least 3000 MET-

minutes/week; moderate if at least 20 minutes of vigorous activity per day for three or more days per week, or at least 30 minutes of moderate intensity activity per day for 5 or more days per week, or five or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving at least 600 MET minutes/week; and finally, when patients did not meet the above criteria, it was classified as low physical activity. Amateurs sportmen/women were only included in the study if they had not participated in any official competition in the last two years.

Cardiovascular magnetic resonance

CMR was performed on a 3T scanner (MAGNETOM® Trio Tim™, Siemens Healthiners, Erlangen, Germany) using retrospective ECG gating and a dedicated 32-element phased-array receiver coil. Contiguous short-axis cine images covering both ventricles from base to apex were acquired using a standard steady-state free-precession sequence (slice thickness 8 mm, 2 mm interslice gap) during breath hold. Also, long-axis cine images of 4-, 3- and 2-chamber views were acquired. Flow imaging was performed perpendicular to the main pulmonary artery and of the ascending aorta with a velocity-encoded gradient echo sequence. Forty phases were acquired and encoded velocities were adjusted to the limit range without aliasing. Finally, delayed enhancement imaging was performed 15 minutes after the administration of 0.15 mmol/Kg of gadobutrol (Gadovist®, Bayer Hispania), using a standard inversion-recovery fast gradient-echo sequence matching short axis cine sequence. All images were stored on a digital archive for post processing. Analysis was performed with dedicated software (Argus (Siemens, Argus, Siemens Medical Solutions, Germany) and Segment® (Medviso AB, Lund, Sweden[5]). Epicardial and endocardial borders were traced in each cine image to obtain left ventricular (LV) volume, sphericity, ejection fraction, mass and relative wall thickness. In order to calculate the parameters corresponding to the right ventricle (RV), the endocardial contours of it were drawn at the end of diastole and systole. Right and left atrial areas were planimetered in the cine 4-chamber view.

Ventricular shapes

A 3D model of the whole heart was constructed with a in-house customized software using a deformable template to fit the CMR short axis, using a previously described algorithm.[6-7] From this model, the endocardial surface of the RV and both the endocardium and epicardium of the LV in end-diastole were extracted. Those 3D surfaces were scaled by BSA, and positioning variability was removed using Procustes Algorithm.[8] Shape analysis was done using Point Distribution Model (PDM), which associates each shape with a vector concatenating all the coordinates of the shape vertices.

The biventricular score was obtained by quantifying the remodeling captured by the biventricular shape models. It was derived from the logistic regression model that predicts SGA from shapes, taking into account the confounding variables (BSA, age and gender). The score corresponds to the logarithm of the odds ratio of the model, after discarding the coefficients that were not associated with the shape (ie, those associated confounding variables and intercept). The score was subsequentially normalized to have 0 mean and unitary standard deviation.

Mathematically, if X^j represent the shape of the j-th patient (which is a vector), then, the probability of the patient j being an SGA can be expressed using the logistic regression model, where β are the coefficients:

$$P(Y^j = 1) = \; logit\left(\sum \beta_i X_i^j + \beta_{age} age^j + \beta_{bsa} bsa^j + \beta_{sex} sex^j + \beta_0\right)$$

Then, the biventricular score Z of the j-th individual was defined as:

$$Z^j = \sum \beta_i X_i^j$$

Incremental exercise testing

Subjects completed standard incremental cardiopulmonary exercise testing on an electromagnetically braked cycloergometer (Ergoselected 100, Ergoline, Bitz, Germany) (rage 6-999 watts) breath-by-breath

using computer-based exercise systems (Ergocard Proffesional, Medisoft, Sorinnes, Belgium). Cycle-ergometer seat adjustments, ECG monitoring and safety measures were standardized in accordance with published guidelines.[9] Standard written and oral instructions were provided to the participants regarding communication during the test safety and what was expected from the subject along the test.[9-10] The incremental test consisted of a 2-minute resting period, followed by 1 minute of unloaded pedaling after which the power was progressively increased. Finally, 2 minutes of the recovery phase were also recorded. Patients wore a low dead-space face mask adapted to the size of their faces (mask 7450 Series Silicone V2™ (Hans Rudolph, Shawnee, KS, USA)). Calculation of the incremental ramp was carried out in a personalized way.[11] The speed of the ramp was calculated for a test duration of about 10 minutes.[9] The speed of the ramp was calculated according the following formula[12]:

- Unloaded oxygen uptake (VO_2) (L·min-1) = 0.15+(0.006 x weight in kg)

- estimated VO_2 (L·min-1) = (height in cm –age in years) x 0.02 (male) y 0.014 (female)

- Ramp= (VO_2 peak - VO_2 unloaded) x 10

VO_2 in L · min-1 and carbon dioxide production (VCO_2) in L · min-1 were measured at standard temperature and pressure dry (STPD). Data were averaged every 10 seconds and correction for the dead-space was applied. The last 10 seconds average was considered to be representative of the subject's peak VO_2. Criteria for a peak test were the observation of a VO_2 plateau or a respiratory exchange ratio (RER)> 1,1 together with a heart rate > 90% of predicted (220 - age in years) and the subjective observation by the conductors of a good subject performance. Oxygen pulse was calculated as VO_2 divided by heart rate. The cause of termination was recorded as stated by the patient as dyspnea, fatigue/leg fatigue, chest pain or others.[13] Blood pressure (both at rest and at peak exercise) was measured always following the same methodology using with a calibrated sphygmomanometer while sitting in the cycloergometer. All measurements were performed according to the international recommendations and reference values.[14]

eAppendix. Results: Smoking Status in the Study Populations

Controls and SGA smokers showed a similar time of exposure (controls median time 15.5 years (IQR 14-20)) vs. SGA 15 years (10.5-19.5), p=0.95) and quantity of cigarettes (Proportion of smokers in the two study populations: 45.5% controls vs 41.7% SGA smokers of <10 cigarettes/day; 40.9% controls vs 41.7% SGA smokers of 11-20 cigarettes/day; 9.1% controls vs 12.5% SGA smokers of 21-30 cigarettes/day; and 4.5% controls vs 4.2% SGA smokers of >30 cigarettes/day; p-value 0.983).

eFigure 1. CONSORT Flow Diagram of the Study

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┌─────────────────────────┐
│ Deliveries from 1975 to 1995 │
│        n=32,490          │
└─────────────────────────┘
            │
            ▼
     ┌──────────────┐
     │  contacted   │
     │   n=532      │
     └──────────────┘
            │              ┌─────────────────────────────────────┐
            │─────────────▶│ 287 refusals                        │
            │              │ 87 exclusions                       │
            │              │     25 current pregnancy            │
            │              │     17 twin pregnancy               │
            │              │     16 neonatal macrosomia          │
            │              │     11 major mental disorder        │
            │              │     10 congenital malformations     │
            │              │     5 genetic syndromes             │
            │              │     3 professional sport practice   │
            │              └─────────────────────────────────────┘
            ▼
     ┌──────────────┐
     │  included    │
     │   n=158      │
     └──────────────┘
        │        │
        ▼        ▼
  ┌──────────┐ ┌──────────┐
  │ Controls │ │  SGA     │
  │  n=77    │ │  n=81    │
  └──────────┘ └──────────┘
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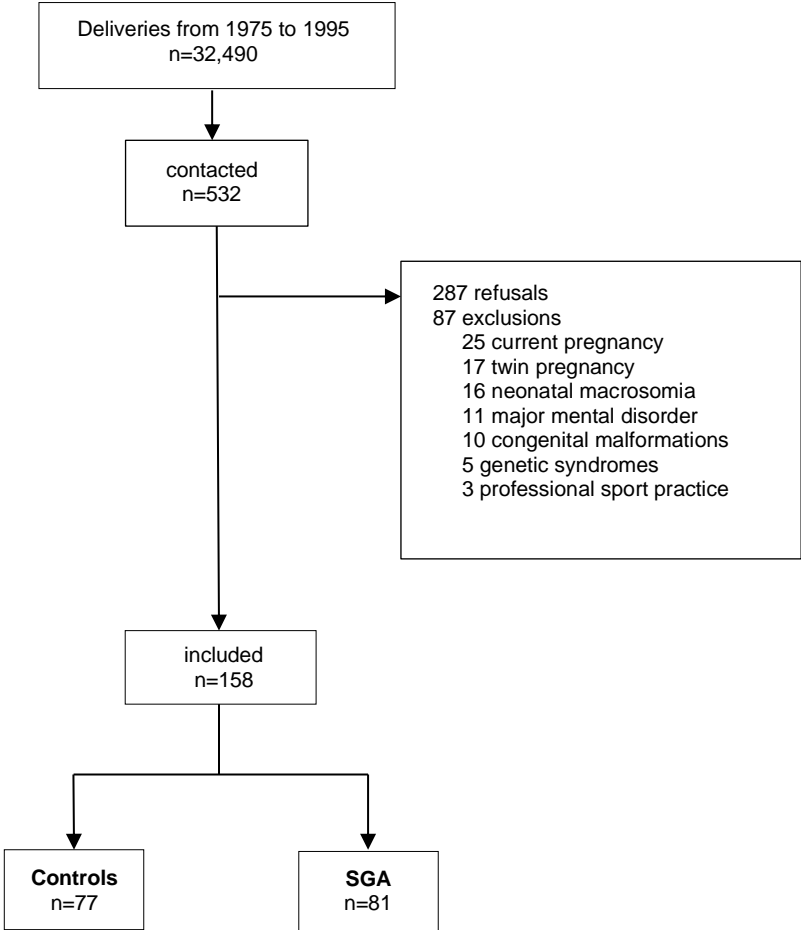
eFigure 2. Baseline Cardiac Structure of Individual Examples

Cardiac magnetic resonance (CMR) images in a control subject and a small for gestational age (SGA) case subject. Four-chamber (top) and three-chamber left ventricular (LV) outflow tract (bottom) views at end-diastole illustrating a flattening of the basal septum and enlargement of the basal portion of RV, that increases the basal RV curvature (red arrows) in SGA.
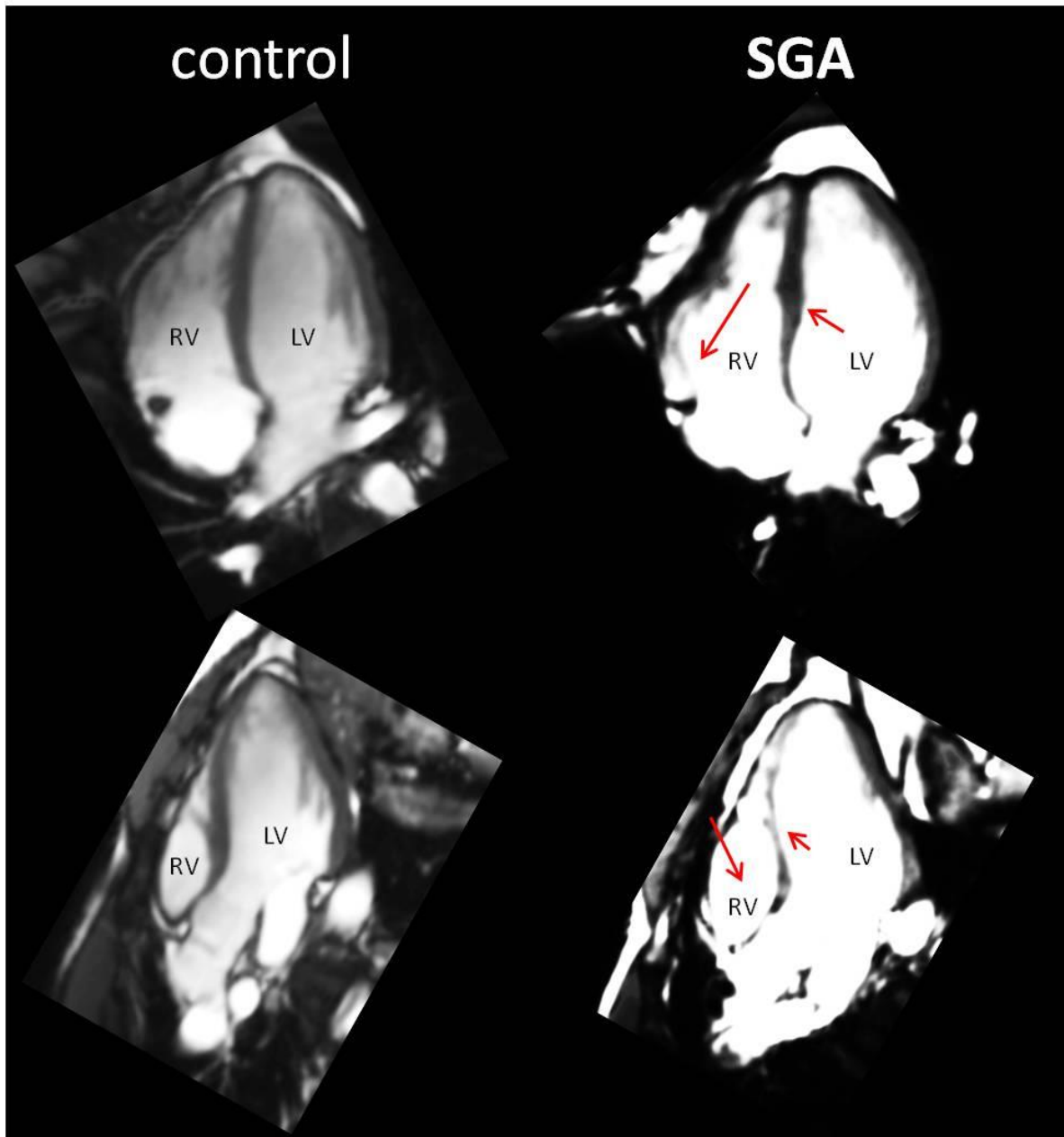
eFigure 3. Population-Derived Representative Reconstructed Ventricular Shapes Depicting a Mean Control and an Extreme SGA Based on the Results of the Statistical Shape Analysis on the Ventricular Surfaces

The left column depicts the surface resulting of averaging the ventricular surfaces of the control population. The right column depicts an extreme SGA, obtained by adding to the mean control the "SGA" shape pattern. The reddish color map shows the places with more differences of SGA as compared to the control, that are mostly concentrated in the RV. An increased RV curvature at the lateral-posterior base and infundibulum could be observed in SGA as compared to controls.
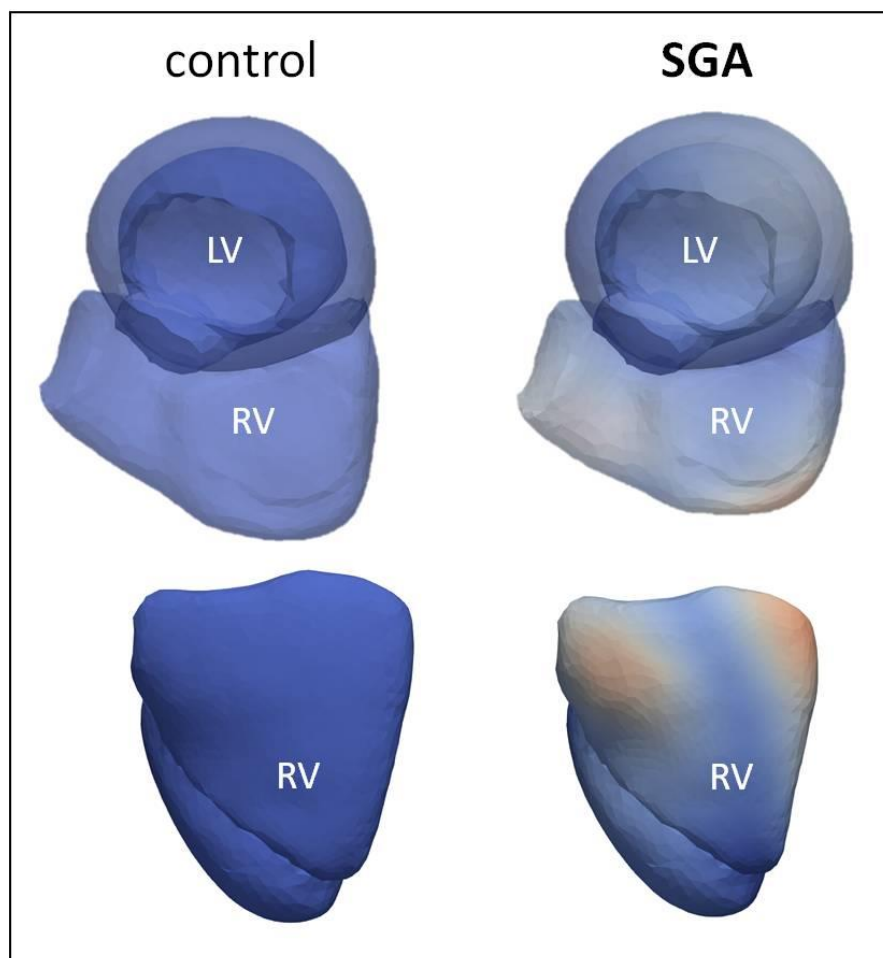
eTable 1. Non-Indexed Cardiac Dimensions and Volumes by Magnetic Resonance

	Controls (n=77)	SGA (n=81)	*p-value*	*adjusted p-value**
Left morphometry				
LVEDV, median (IQR), mL	160.7 (138.3-188.5)	145.4 (129.1-161.9)	*0.002*	*0.048*
LVESV, median (IQR), mL	62.8 (50.7-77.4)	62 (48-68.5)	*0.120*	*0.936*
LV base-to-apex length, median (IQR), mm	9.1 (8.7-9.7)	9.1 (8.4-9.4)	*0.010*	*0.032*
LV basal diameter, median (IQR), mm	47.3 (43.3-50.7)	44.9 (42.9-47.5)	*0.002*	*0.046*
LV mass, mean (SD), g	90.2 (27.1)	80.7 (21.3)	*0.023*	*0.480*
Left atrial area, mean (SD), cm^2	23.6 (3.3)	21.8 (3.8)	*0.001*	*0.053*
Aortic area, mean (SD), cm^2	6.7 (1.3)	6.5 (1.5)	*0.214*	*0.599*
Right morphometry				
RVEDV median (IQR), mL	147 (122.8-168.9)	126.8 (113.1-147.6)	*0.001*	*0.047*
RVESV, median (IQR), mL	67.1 (50.2-81.5)	55.5 (46-68)	*0.001*	*0.007*
Right atrial area, mean (SD), cm^2	21.3 (4.9)	18.2 (4)	*0.001*	*0.011*
Maximal pulmonary artery area, mean (SD), cm^2	7.2 (1.3)	6.6 (1.4)	*0.014*	*0.048*

SGA indicates small-for-gestational age; LV, left ventricle; RV, right ventricle; EDV, end-diastolic volume; and ESV, end-systolic volume.
*P-value as compared to controls adjusted by age, gender, body surface area, asthma, education, smoking habit, gestational age at delivery, breastfeeding and gestational hypertension.

eTable 2. Cardiac Magnetic Resonance Results According to Standard Deviations From the Mean

Reference Values (Z-Scores)

	Controls (n=77)	SGA (n=81)	P-value
Left morphometry			
LVEDV/BSA, mean (SD), z-score	0.3 (1.1)	0.1 (0.8)	*0.389*
LVESV/BSA, mean (SD), z-score	0.9 (1)	1 (0.9)	*0.492*
LV mass, mean (SD), g/m^2	-0.8 (0.9)	-1.1 (0.8)	*0.073*
Right morphometry			
RVEDV/BSA, mean (SD), mL/m^2	-1.1 (1)	-1.3 (1)	*0.151*
RVESV/BSA, median (IQR), z-scores	-0.1 (-0.7 to 0.5)	-0.4 (-1 to 0.2)	*0.033*
LV function			
LV ejection fraction, median (IQR), z-score	-0.9 (-1.6 to -0.3)	-1.2 (-1.9 to -0.6)	*0.043*
RV function			
Right ejection fraction, median (IQR), z-score	-1 (-1.5 to -0.5)	-0.8 (-0.7 to -1.3)	*0.051*

Z-scores calculated as: (individual result – mean of the population) / SD of the population, according to published reference values.[15]

eTable 3. Heart Rate and Blood Pressure Results at Baseline, Anaerobic Threshold and Peak Exercise in

the Study Populations

		Controls (n=66)	SGA (n=61)	p-value	adjusted p-value*
Heart rate, median (IQR), bpm	Baseline	77.5 (69-85)	80 (72-90)	0.354	0.323
	Anaerobic threshold	120 (112-129	122 (115-135)	0.339	0.481
	Peak exercise	176 (168-185)	176 (165-184)	0.755	0.623
	Delta change peak-baseline	*100.5 (86-109)*	*96 (82-107)*	0.293	0.227
Systolic blood pressure, median (IQR), mmHg	Baseline	115 (105-125)	116 (108-126)	0.354	0.145
	Peak exercise	179.5 (162-203)	171 (144-186)	0.034	0.039
	Delta change peak-baseline	*72 (47-87)*	*56 (3867)*	0.005	0.026
Diastolic blood pressure, median (IQR), mmHg	Baseline	74.5 (69-84)	76 (68-84)	0.814	0.617
	Peak exercise	90 (84-100)	89 (80-102)	0.856	0.547
	Delta change peak-baseline	*14.5 (7-27)*	*17 (7-26)*	0.987	0.849
Pulse pressure, median (IQR)	Baseline	38 (31-45)	38 (33-46)	0.739	0.897
	Peak exercise	90 (75-108)	75 (56-90)	0.008	0.048
	Delta change peak-baseline	49 (35-68)	43 (18-54)	0.006	0.033

*P-value as compared to controls adjusted by age, gender, body surface area, asthma, education, smoking habit, gestational age at delivery, breastfeeding and gestational hypertension.

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