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Prevalence of renal dysfunction and its influence on functional capacity in elderly patients with stable chronic heart failure

Učestalost bubrežne disfunkcije i njen uticaj na funkcionalni kapacitet kod starijih bolesnika sa hroničnom stabilnom insuficijencijom srca

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Abstract

Bacground/Aim. Chronic heart failure (CHF) is highly prevalent and constitutes an important public health problem around the world. In spite of a large number of pharmacological agents that successfully decrease mortality in CHF, the effects on exercise tolerance and quality of life are modest. Renal dysfunction is extremely common in patients with CHF and it is strongly related not only to increased mortality and morbidity but to a significant decrease in exercise tolerance, as well. The aim of our study was to investigate the prevalence and influence of the renal dysfunction on functional capacity in the elderly CHF patients. **Methods.** We included 127 patients aged over 65 years in a stable phase of CHF. The diagnosis of heart failure was based on the latest diagnostic principles of the European Society of Cardiology. The estimated glomerular filtration rate (eGRF) was determined by the abbreviated Modification of Diet in Renal Disease (MDRD2) formula, and patients were categorized using the Kidney Disease Outcomes Quality Initiative (K/DOQI) classification system. Functional capacity was determined by the 6 minute walking test (6MWT). **Results.** Among 127 patients, 90 were men. The average age was 72.5 ± 4.99 years and left ventricular ejection fraction (LVEF) was 40.22 ± 9.89%. The average duration of CHF was 3.79 ± 4.84 years. Ninty three (73.2%) patients were in New York Heart Association (NYHA) class II and 34 (26.8%) in NYHA class III. Normal renal function (eGFR ≥ 90 mL/min) had 8.9% of participants, 57.8% had eGFR between 60–89 mL/min (stage 2 or mild reduction in GFR according to K/DOQI classification), 32.2% had eGFR between 30–59 mL/min (stage 3 or moderate reduction in GFR) and 1.1% had eGFR between 15–29 mL/min (stage 4 or severe reduction in GFR). We found statistically significant correlation between eGFR and 6 minute walking distance (6MWD) ($r = 0.390$, $p < 0.001$), LVEF ($r = 0.268$, $p < 0.05$), NYHA class ($\varrho = -0.269$, $p < 0.05$) and age ($r = -0.214$, $p < 0.05$). In multiple regression analysis only patients' age was a predictor of decreased 6MWD < 300 m (OR = 0.8736, CI = 0.7804 - 0.9781, $p < 0.05$). **Conclusion.** Renal dysfunction is highly prevalent in the elderly CHF patients. It is associated with decreased functional capacity and therefore with poor prognosis. This study corroborates the use of eGFR not only as a powerful predictor of mortality in CHF, but also as an indicator of the functional capacity of cardiopulmonary system. However, clinicians underestimate a serial measurement of eGFR while it should be the part of a routine evaluation performed in every patient with CHF, particularly in the elderly population.

Key words:
heart failure; aged; kidney failure; glomerular filtration rate; quality of life.

Apstrakt

Uvod/Cilj. Srčana insuficijencija (SI) je značajan zdravstveni problem koji ima epidemijske razmere. U terapiji SI koriste se mnogobrojni lekovi koji utiču na smanjenje mortaliteta. Međutim, oni ne popravljaju značajno funkcionalni kapacitet i kvalitet života. Bubrežna disfunkcija, često prisutna kod bolesnika sa SI, značajno je udružena sa povećanim morbiditetom i mortalitetom, ali i sa smanjenim funkcionalnim kapacitetom. Cilj istraživanja bio je da se utvrdi učestalost bubrežne disfunkcije i njen uticaj na funkcionalni kapacitet kod starijih bolesnika sa stabilnom SI. **Metode.** U istraživanje je bilo uključeno 127 bolesnika, starijih od 65 godina u stabilnoj fazi SI. Funkcionalni kapacitet određivan je pomoću 6-minutnog testa hodom, glomerularne filtracije (GFR) pomoću skraćene *Modification of Diet in Renal Disease* (MDRD) formule. **Rezultati.** Od ukupno 127 bolesnika u stabilnoj fazi SI (prosečnog trajanja 3,79 ± 4,84 godina), funkcionalne *New York Heart Association* (NYHA) klase II ili III, 90 je bilo muškog pola. Njihova prosečna starost iznosila je 72,5 ± 4,99 godina, a prosečna ejekciona frakcija (EF) 40,2 ± 9,9%. Normalnu bubrežnu funkciju imalo je 8,9%

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ispitanika, 57,8% bolesnika imalo je lako smanjenu GFR [stadijum 2 prema *Kidney Disease Outcomes Quality Initiative* (K/DOQI klasifikaciji), 32,2% imalo je umereno redukovanu GFR (stadijum 3) dok je 1,1% bolesnika imalo teško redukovanu GFR (stadijum 4)]. Nađena je značajna korelacija između GFR i rastojanja pređenog tokom 6-minutnog testa hodom ($r = 0,390$, $p < 0,01$), EF ($r = 0,268$, $p < 0,05$), NYHA klase ($\varrho = -0,269$, $p < 0,05$) i životnog doba ($r = -0,214$, $p < 0,05$). Jedini prognostički pokazatelj rastojanja pređenog tokom 6-minutnog testa hodom ispod 300 m bila je starost bolesnika (OR = 0,8736, CI = 0,7804 – 0,9781, $p < 0,05$). **Zaključak.** Najveći broj ispitanika imao je bubrežnu disfunkciju koja je bila udružena sa smanjenim funkcionalnim kapacitetom koji je u SI udružen sa lošom prognozom. Serijsko određivanje GFR trebalo bi da bude rutinski deo kliničkog pregleda svih bolesnika sa SI, posebno starijih.

Ključne reči:
srce, insuficijencija; stare osobe; bubreg, insuficijencija; glomerulska filtracija; kvalitet života.

Introduction

Chronic heart failure (CHF) is a disorder associated with high mortality and persistent and prolonged hospitalizations, and affects over 10 million people in the countries represented by the European Society of Cardiology. The prevalence of CHF increases markedly with age when the treatment is often complicated by the presence of multiple comorbidities [1]. A significant portion, up to 39% of patients with CHF, also has renal insufficiency, and the prevalence increases with the age. Renal insufficiency is directly associated with morbidity and mortality independent on established risk factors such as New York Heart Association (NYHA) class and left ventricle ejection fraction (LVEF) [2, 3]. Chronic heart failure is now seen not only as a cardiac disorder but rather a cardiorenal and neurohumoral syndrome which affects quality of life more profoundly than many other chronic diseases [4, 5].

Survival in heart failure is closely related to functional capacity and some studies suggest that quality of life is a predictor of CHF course [6, 7]. Patients' functional status and ultimately quality of life are impaired because the heart is unable to meet the demands of skeletal musculature, and symptoms manifest as signs of fatigue and dyspnea even in patients with guideline-based optimized therapy. Abnormalities in central hemodynamic function are not sufficient to fully explain exercise intolerance in CHF because indices of resting ventricular function such as LVEF are poorly correlated with peak exercise capacity [1, 8, 9].

However, not only heart failure, but advanced age and renal dysfunction both closely related, have influence on functional capacity [10]. The HF-ACTION trial showed that reduced renal filtration is associated with impaired cardiorespiratory fitness and a clustering of high-risk features in systolic heart failure patients which portend a more complicated course and higher all-cause mortality [11].

The 'gold standard' method for the assessment of functional capacity is the cardiopulmonary exercise test (CPET). However, CPET equipment is expensive and cumbersome, and availability of trained staff is limited. A simple, self-paced, and submaximal alternative is the 6 minute walk test (6MWT) [12]. It is commonly used, and is both reproducible and cheap to administer [1].

The aim of our study was to assess the prevalence of renal dysfunction and its influence on functional capacity in elderly patients with stable CHF.

Methods

In our study we included 127 consecutive patients aged over 65 years in a stable phase of CHF (2 weeks without worsening of cardiovascular symptoms and without changes in medical treatment or need for intravenous inotropic support) who were recruited during the scheduled visit to the cardiologist. The diagnosis of heart failure was based on the latest diagnostic principles of the European Society of Cardiology (ESC) [13]. We enrolled patients with systolic (LVEF ≤ 45%) and diastolic heart failure with NYHA function class II and III with at least of one episode of acute cardiac decompensation. Echocardiography measurements were performed on the Vivid 4, GE ultrasound system and LVEF was measured according to the Simpson's biplane method. Serum creatinine concentration was measured by the Jaffé method (alkaline picrate reaction) with laboratory referent values 53–115 μmol/L. It is often quoted as a barometer of renal impairment, but it is actually a poor indicator of renal function. Therefore, estimation of the glomerular filtration rate (eGFR) is preferred for the accurate assessment of renal function [4, 10]. The eGFR was determined by the abbreviated Modification of Diet in Renal Disease (MDRD) formula and patients were categorized using the Kidney Disease Outcomes Quality Initiative (K/DOQI) classification system [14]. The abbreviated MDRD formula provides valid estimation of glomerular filtration rate (GFR) and according to recent findings it is superior to the Cockcroft-Gault formula [4, 15–18]. According to the World Health Organization (WHO) anemia is defined as hemoglobin (Hb) concentration < 13.0 g/dL in men and < 12.0 g/dL in women [19]. The presence of chronic obstructive pulmonary disease (COPD) was assessed according to the definition of Global Initiative for COPD – „GOLD" criteria: spirometrically assessed ratio of a post-dilatory forced expiratory volume in the first second divided by forced vital capacity (FEV1/FVC), the so-called Tiffno index, less than 70% [20]. The functional capacity was determined by the 6MWT. 6MWT was performed on flat floor, being 25 meters on straight line. The patients were instructed to walk at their own pace while attempting to cover as much ground as possible in 6 minutes. After 6 minutes the distance walked was measured to the nearest meter. The study was performed in Clinic for Cardiovascular Disease, Clinical Center Niš. The study complied with the Declaration of Helsinki. The Medical Ethical Committee of the Faculty of Medicine, University of Niš, Niš, Serbia, approved the study protocol. All participants submitted written informed consent.

Data are presented as mean ± standard deviation (SD) for continuous measures and as a proportion for categorical variables. We used Pearson's correlation coefficient (r) for variables with normal distribution and Spearman's *rho* correlation coefficient (ρ) for ordinal variables. Multiple regression analysis was used to determine predictors of reduced 6MWD and therefore, decreased functional capacity. All the values of p were two-tailed and statistical significance was established as $p < 0.05$. Statistical analysis was completed using the SPSS software, version 17.0 for Windows.

Results

Among 127 patients, 90 (70.9%) were men. The baseline patients' characteristics are presented in Table 1. The average age was 72.5 ± 4.99 years and LVEF was 40.22 ± 9.89%. The average duration of CHF was 3.79 ± 4.84 years. Ninty three (73.2%) patients were in NYHA class II and 34 (26.8%) in NYHA class III. Only 17 (13.38%) patients had diastolic heart failure (heart failure with preserved LVEF). Comorbidities and previous medical procedures are presented in Table 2. The etiology of heart failure is presented in Table 3. Twenty four (18.9%) patients had anemia (the lowest value of hemoglobin was 98 g/L) and 17 (13.38%) patients had COPD (the average value of Tiffno index was 0.61). They were on stable medical therapy during at least 2 weeks before inclusion in the study (Table 4). Only 8.9% of the participants had eGFR ≥ 90 mL/min, 57.8% had eGFR between 60–89 mL/min (stage 2 or mild reduction in GFR according to K/DOQI classification), 32.2% had eGFR between 30–59 mL/min (stage 3 or moderate reduction in GFR) and 1.1% had eGFR between 15–29 mL/min (stage 4 or severe reduction in GFR) (Figure 1). Figure 2 shows a scattered diagram with creatinin values grouped in the adequate K/DOQI class. We correlated all the relevant factors with the 6MWD and eGFR including LVEF, NYHA class, age, gender, body mass index (BMI), heart rate (HR),

Table 3
Etiology of heart failure in the patients included in the study

Etiology of CHF	n (%) of patients
Ischemic heart disease	86 (67.6)
Arterial hypertension	30 (23.8)
Dilated cardiomyopathy	9 (7.4)
Valvular disease	2 (1.2)

Table 4
Cardiovascular medical treatment of the patients included in the study

Medication	n (%) of patients
ACE inhibitors	107 (84.5)
Beta blockers	127 (100)
Antiplatelet agents	105 (82.5)
Anticoagulants (vitamin K antagonist)	41 (32)
Digoxin	33 (25.8)
Diuretics	90 (71.1)
Spironolacton	60 (47.4)
Nitrates	63 (49.5)
Calcium antagonists	26 (20.6)
Statins	43 (34)
Amiodaron	14 (11.3)

Table 1
The baseline characteristics of the patients included in the study

Characteristics	Mean ± SD	Min– Max
Age (years)	72.5 ± 4.996	63–86
Duration of CHF (years)	3.79 ± 4.836	0–11
LVEF (%)	40.22 ± 9.887	20–75
6MWD (m)	307.31 ± 100.055	60–513
Serum creatinine (μmol/L)	102.26 ± 31.820	66–281
eGFR (mL/min)	66.17 ± 18.451	15–109
Haemoglobin (g/L)	137.41 ± 14.948	98–172
BMI (kg/m^2)	26.55 ± 3.720	19–38
HR (/min)	72.77 ± 12.190	53–129
FEV1/VC (Tiffno index)	0.74 ± 0.094	0.43–0.96

CHF – chronic heart failure, LVEF – left ventricle ejection fraction, 6MWD – six minute walk distance, eGFR – estimated glomerular filtration rate, BMI – body mass index, HR – heart rate

Table 2
Comorbidities and previous medical procedures in patients included in the study

Comorbidities and previous medical procedures	n (%) of patients
Diabetes mellitus	38 (30.1)
Arterial hypertension	92 (72.6)
Dyslipidemia	54 (42.5)
COPD	17 (13.38)
Coronary artery disease	96 (75.7)
Previous myocardial infarction	76 (60.2)
Previous percutaneus coronary intervention	10 (8)
Previous coronary artery bypass surgery	18 (14.2)

COPD – chronic obstructive pulmonary disease

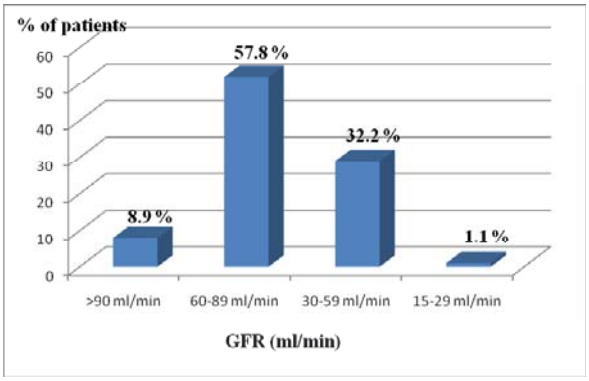

Fig. 1 – Percentage of patients with different stages of renal dysfunction

eGFR – estimated glomerular filtration rate

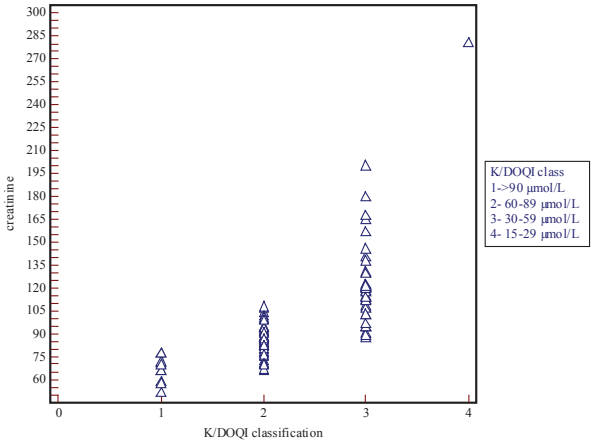

Fig. 2 – Scattered diagram with creatinine values grouped in the adequate Kidney Disease Outcomes Quality Initiative (K/DOQI) class

hemoglobin level, and the presence of COPD, systolic or diastolic heart failure. A statistically significant correlation was found between eGFR and 6MWD (r = 0.390, $p < 0.01$) (Figure 3), LVEF (r = 0.268, $p < 0.05$), NYHA class (ρ = -0.269, $p < 0.05$), age (r = -0.214, $p < 0.05$) and female gender (ρ = -0.388, $p < 0.01$). However, there was no significant correlation between 6MWD and creatinine (r = -1.75, $p = 0.1$; linear regression, $R^2 = 0.03$, $p = 0.1$) (Figure 4). Six-minute walk distance correlated with NYHA class (ρ = -0.231, $p < 0.05$), age (r = -0.245, $p < 0.01$) and female gender (ρ = - 0.446, $p < 00.01$), as well. In multiple regression analysis (where we included age, gender, the presence of COPD, anaemia, eGFR, NYHA class, LVEF) only patients' age was a predictor of decreased 6MWD < 300 m (OR = 0.8736, 95%, CI = 0.7804 - 0.9781, $p < 0.05$). The probability of reducing the 6MWD < 300 m increased by 8.7% with every year of age.

Discussion

Heart failure plays an important role in public health, being one of the major complications of heart disease and a leading cause of death in developed countries. The natural history of this illness constitutes impairment of functional capacity, physical performance, and ability to perform daily activities, finally becoming detrimental to the quality of life [9].

Concomitant and significant renal dysfunction is common in patients with heart failure [21, 22]. In the study of Waldum et al., [23] 44.9% of the elderly outpatients with heart failure had eGFR lower than 60 mL/min. Accordingly, in our study 91.1% of patients had renal dysfunction and among them 33.3% had moderate or severe renal dysfunction (eGFR < 60 mL/min). For adequate interpretation of epidemiological studies it is essential to use the universal definitions of renal dysfunction (GFR = 60–89 mL/min), renal impairment and chronic kidney disease (GFR below 60 mL/min for at least 3 months, among other criteria) [14]. As patients with advanced heart failure are also likely to have an element of renal dysfunction, it is of interest to know how prognostically relevant this is. Renal impairment is often associated with CHF owing to renal hypoperfusion, diuretic treatment, disease-modifying heart failure therapy (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, aldosterone antagonists), as well as other concomitant medication and comorbidities [4]. Scardovi et al. [24] showed that renal dysfunction in elderly CHF patients is a main independent prognostic predictor across the spectrum of ventricular impairment indices. Although the pathogenesis of reduced GFR may differ between patients and even over

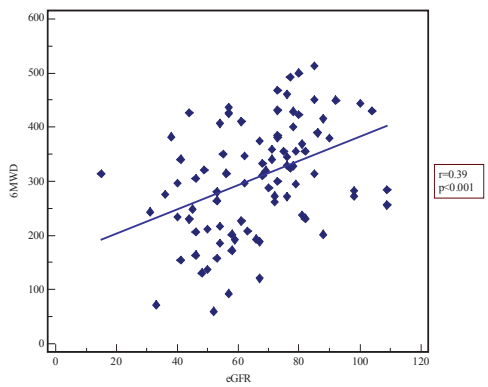

Fig. 3 – Correlation between eGFR and 6MWD

eGFR – estimated glomerular filtration rate

6MWD – 6-minute walk distance

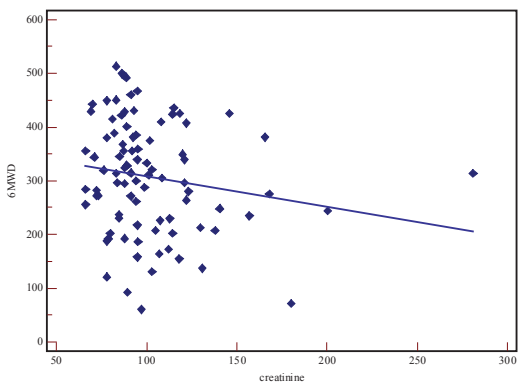

Fig. 4 – Linear regression line [influence of creatinine on 6-minute walk distance (6MWD)]

time within an individual, the result is the same: reduced GFR is strongly related to increased mortality and morbidity and impaired functional capacity in CHF.

In our study we found a significantly positive correlation between eGFR and 6MWD, while NYHA class, female gender and age inversely correlated with eGFR which is in accordance with previous reports [11, 25, 26]. A positive correlation was found between LVEF and eGFR. Although a greater proportion of patients with low eGFR have a worse NYHA class, no evidence of association between LVEF and eGFR can be consistently demonstrated. Thus, patients with systolic and diastolic CHF appear to have similar eGFR [27].

Functional capacity provides a strong independent insight into the prognosis of patients with heart failure. Information on peak oxygen consumption (PvO_2) during cardiopulmonary exercise testing is used extensively to evaluate cardiovascular performance. Several studies have supported PvO_2 as an independent prognostic index of survival in patients with heart failure [28].

The 6MWT has been proposed as a simple, inexpensive, reproducible alternative to CPET. The test showed a good reproducibility and a significant relation between the distance walked during the test and the PvO_2 and, respectively, survival has been demonstrated. The 6MWT reproduces the activity of daily life and this is particularly relevant in elderly patients who usually develop symptoms below their theoretical maximal exercise capacity [6]. We determined a significant inverse correlation between 6MWD, NYHA class, age, female gender and renal dysfunction (eGFR) which is in accordance with findings of Ingle et al. [12]. However, hemoglobin concentration, BMI, resting heart rate and the presence of COPD did not correlate with 6MWD which is not in line with previous reports [12, 29]. However, the lowest value of hemoglobin was 98 g/L, which means that our patients had very mild anemia. Furthermore, our patients with COPD had the average Tiffno index of 0.61 and therefore mild COPD, which could partially explain the effect of those comorbidities on functional capacity. In our study 6MWD significantly correlated with LVEF, and there was no significant difference between patients with systolic or diastolic heart failure, which is in line with published literature [27, 30]. It has been demonstrated that a walking distance less than 300 m during the 6MWT is an independent predictor of long-term mortality in patients with mild-to-moderate heart failure [28, 31]. In our study, multiple regression analysis showed that only patients' age was a predictor of reduced 6MWD < 300 m. However, only 47.8% of our patients had 6MWD below 300 m, so more than 50% of our patients were not included in this analysis. In the HF-ACTION study age was the strongest predictor of PvO_2 and a significant predictor of exercise capacity. Age-dependent comorbidities, such as renal dysfunction, do not explain changes in PvO_2. Age-related changes in cardiovascular physiology, potentially magnified by the CHF, should be considered as a contributor to the pathophysiology and a target for more effective therapy in older patients with CHF [32].

A number of biologically diverse chronic illnesses such as renal failure, COPD and congestive heart failure result in a significant decrease in exercise tolerance. In each of these disease states, treatments aimed at the primary pathology have provided powerful palliative effects. However, in general, improvements in exercise tolerance following such interventions are delayed and incomplete. This has led to an increasing awareness that secondary treatment strategies, such as prescribed exercise, designed to restore some level of physical performance and quality of life can be beneficial [33]. The American Heart Association has recently taken the position that exercise rehabilitation has an important place in the treatment of heart failure [34]. The potential mechanisms by which CHF and renal dysfunction may negatively impact skeletal muscle are complex, resulting from alterations in muscle perfusion, substrate delivery, and catabolic state mediated by various factors such as metabolic acidosis, corticosteroids, proinflammatory cytokines, and decreased physical activity, among others. In summary, numerous disorders promote skeletal myopathy developement, impaired exercise tolerance, and hence a sedentary lifestyle in CHF patients. Reduction in physical activity, in turn, leads to further decline in muscle mass, progressive disability, and various other untoward consequences. Regular exercise regimens can interrupt this vicious cycle and improve physical condition. Thus the inclusion of exercise as a standard component of care appears to be warranted in the overall management of these patients [33, 35]. Nevertheless, pharmacological management, focused on kidney protection to prevent or slow progression of renal impairment, may improve outcome in elderly HF patients [24].

Conclusion

Renal dysfunction is highly prevalent in elderly CHF patients. It is associated with decreased functional capacity and, therefore, poor prognosis. This study corroborates the use of eGFR not only as a powerful predictor of mortality in CHF, but also as an indicator of the functional capacity of cardiopulmonary system. Large, prospective studies remain to be performated for understanding the etiology of reduced eGFR in patients with CHF. Inclusion of patients with renal insufficiency in heart failure studies and the published guidelines for medication, device, and interventional therapies would likely improve therapeutic outcomes. This will lead to novel therapeutic strategies not only in reducing mortality but also in improving life quality in CHF. However, clinicians underestimate serial measurement of eGFR while it should be a part of routine evaluation initially performed in every patient with CHF, particularly in elderly population.

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