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THE DIAGNOSTIC INTEREST AND STRATIFICATION OF NT-PROBNP IN THE CORONARY SYNDROME

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ABSTRACT

The risk of stratification plays an important role in the management of patients with ACS, and constitutes daily an aid to guide the strategy therapeutic. The natriuretic peptides, reflecting the ventricular dilatation and load conditions, could make a useful additional information. The natriuretic peptides are potent cardiac excess mortality markers in the SCA with or without extra-ST segment. Our objective is to evaluate the natriuretic peptide and several markers to identify patients scheduled to benefit from an early invasive strategy. This is a prospective study of 100 coronary hospitalized at the cardiology department for coronary syndrome. This is a prospective study of 100 coronary hospitalized in the cardiology department for coronary syndrome. The average age of coronary patients was 60.53 ± 12.32 years, with male sex predominance of 63.33%. 65.6% are coronary ST-. The average of NT-pro BNP rate is 2420.50 ± 4279pg / ml and it was related to the age and deterioration of renal function. In the study mono varies NT-proBNP is always associated coronary syndrome in the advancing age, at the injury of renal function, hyponatremia a reverse effect with obesity and the odds ratio is 2.35 (0.99 to 5.62) in the IDM. The NT-proBNP has great diagnostic and prognostic value in the stratification of the coronary syndrome.

KEYWORDS: acute coronary syndromes, N-terminal pro-brain natriuretic peptide, hyponatraemia, obesity.

INTRODUCTION

The coronary syndrome is a cause of death in all countries of the world.[1.2.3] Under the conditions where there is an absence of treatment, the prognosis is fatal SC to either necrosis IDM or towards the mortality.[4.5] Meta-analysis studies have shown the diagnostic and prognostic interest of BNP and NT-proBNP in cardiovascular diseases.[6.7.8] Doust and col have been using in meta-analysis BNP and NT-proBNP; they showed that the two markers are mortality indicators and of IDM in patients with asymptomatic heart failure and in all cardiovascular pathologies.[9]

NT-proBNP (N-terminal peptide probrainnatruiritic) is a cardiac marker, his liberation is related to the stretching or distension ventricular myocyte (mechanical stimuli) by expansion or increase of the volume of the ventricular pressure.[10.11.12.13.14]

NT-proBNP has an important physiological effect; vasodilatation: effect "nitrated" promotes diuresis and natriurès, e: effect "furosemide" opposes at the activity of the renin angiotensin system, an essential role in the sodium and water homeostasis in maintaining plasma volume and regulation blood pressure and reduced vascular peripheral resistance.[15.16] The NT-proBNP is associated with heart failure, left ventricular failure, the coronary syndrome, a high blood pressure and other non-cardiac condition such as cerebrovascular accident and septicemia.[17.18.19]

Other severe conditions like advanced age, medical treatment, renal dysfunction, obesity, hemodynamic change as hypertension as well as to the presence of chronic diseases can affect the levels of NT-proBNP.[20.21.22.23.24] The increase in NT-proBNP levels is found in coronary patients in the absence of ventricular dilation and in the exercises inducing ischemia.[25.26.27]
In coronary syndrome, there is a predisposition to the increased incidence of heart failure and the increase in NT-proBNP levels. These two factors cause hyponatremia that increase the risk of death.[28] Hyponatremia is defined by a concentration of Na <135mmol / l and the electrolyte the most frequently

dosed and disrupted in clinical pathology.[29.30] Hyponatremia is associated with the risk of mortality in several studies; in patients hospilalisés.[30] in patients with renal failure [31],in patients with insufficient cardiaque[32] and the population.[33.34.35] Anemia is a factor that predicts cardiac insufficiency in the Coronary Syndrome. Sometimes in the absence of symptoms of cardiac insufisance, patients who have anemia have levels of NT-proBNP increased.[36] this suggests that anemia causes an asymptomatic cardiac dysfunction (subclinical).

The combination of increased NTproBNP to anemia is explained by the systolic and diastolic cardiac dysfunction, inflammation and heart failure. The presence of anemia may be exacerbated the evolution of coronary syndrome. The evolution of inflammation and same damage of myocardial ischemia.[37]

Our objective is to identified the NT-proBNP association with clinical, radiological and biological parameters in the coronary syndrome and its interest in the stratification of the syndrome.

PATIENTS AND METHODS

Is a prospective study of 100 coronary patients hospitalized at the cardiology service university hospital center Saadna Abdenour Mohamed Setif-Algeria for acute coronary syndrome during the period of January 2014- May 2015. For these patients were analyzed the following parameters:

Formulas blood counts (FNS) for the research of hemoglobin levels, MCHC and MCV (Coulter STAGO). We have assayed the NT-proBNP; by the electro-chimilumenescence method Cobas E411; And we have assayed vitamin B12, B9 and homocysteine by chemical luminescence method Siemens 2000.

Other parameters

We have investigated the age, sex, creatinine, triglycerides rate, Total cholesterol and blood sugar on ADVIA PLC; Troponin hypersensitive Cobas E411.

The search for other risk factors; Hypertension, diabetes, dyslipidemia and smoking; All patients benefited from an ECG in search of acute coronary syndrome ST- or ST +.

All patients benefited from echocardiography to research right ventricular failure or left and the fraction of ejection systolic and diastolic. Clinical examination searching for dyspnea, palpitation, chest pain, syncope.

STATISTIC ANALYSIS

Since the normality is not assured for all of the parameters, we replaced the Student test by the Mann-Whitney and Fischer test (ANOVA) by the Kruskal-Wallis.

The variables of a qualitative nature are subjected to a khi-carré independence test.

RESULTS

Table 1: descriptive study of the global population

Parameters		Parameters	
Age (years)	60.53 ± 12.32	Sex	63.33%
HTA	57.77%	Dyslipidemia	41.11%
Diabetes	40%	Smoking	48.88%
IDM	41.11%	Myocardial ischemia	21.11%
Unstable angina	37.78%	Vitamine B12(pg/ml)	54.27 ±182.20
NT-proBNP(pg/ml)	2420.50±4279l	Hémoglobine	13.63 ±1.96
Homocysteine(µmol/l)	17.97 ± 16.56	RDW	11.47±7.06%
Vitamin B9(ng/l)	8.48 ± 5.81	Creatinine	10.09 ± 2.98
Blood sugar (g / l)	1.38 ± 0.63 g / l	Natremia	135±3.94
Cholesterol T (g / l)	1.52 ± 0.42 g / l	Troponin HS	0.22 ± 0.26
Triglyceride (g / l)	1.55 ± 0.78	Syncope	5.55%
Urea	0.43 ± 0.23	IVG	26%
Dyspnea	48%	IVD	3.33%
Chest pain	73.33%	Ejection fraction	50%
ST -	65.6%	Other	34.4
ST +	34.44%		

Table 2: The Pearson coefficient of correlation (r) and significance level (p) of the various parameters with NT-pro BNP.

Parameters	NT-pro BNP	
	Pearson Correlation (r)	Significant
Age	**0.23**	**0.024**
Glycemia	0.108	0.311
Cholesterol	-0.57	0.59
Tryglyciride	-0.91	0.39

Creatinine	**0.37**	**0.043**
Urea	**0.27**	**0.041**
ASAT	0.17	0.10
ALAT	0.15	0.14
Hs Troponin	0.27	0.8
Homocysteine	0.16	0.27

For the whole population, we are observed that the following significant correlation:
NT-pro BNP has a positive correlation with creatinine and urea.

Table 3: statistical association of NT-proBNP to different cardiovascular risk factors in coronary syndrome (Khi2)

	Global	**NT-proBNP<900**	**NT-proBNP>=900**	**Khi2 (p)**
Age	60.477±12.94	57.62±13.41	64.27±11.57	0.008
Sex %M	65.5	72	58	0.186
HTA %	57.77	52.9	59.5	0.543
Diabete %	40	43.1	48.6	0.608
Dyslipidemia %	41.11	35.3	43.2	0.314
Smoking %	48.8	52.9	43.2	0.369
IDM	41.11	30.3	57.43	0.049
Myocardial ischemia	21.1	23.5	16.2	0.401

Table 4: Association of NT-proBNP to various clinical and radiographic factors in coronary syndrome

	Global	**NT-proBNP<900**	**NT-proBNP>=900**	**Khi2 (p)**
IC(FE) % <0.50	50	11	39	0.032
IVG	26	9	17	0.045
coronary syndrome ST +	35	13	18	0.42
coronary syndrome ST -	65	42	23	0.042
dyspnea	48	16	35	0.023

Table 5: On the threshold of 900 pg / mL according to age and sex, a very good sensitivity is obtained (77%) and a very good PPV (80.50%).
EF = ejection fraction of the left ventricle

Threshold of NT-proBNP	**Sensitivity**	**Specificity**	**Sensitivity + specificity**	**positive predictive value**	**negative predictive value**
300	76.36	50	126.36	71.18	56.66
450	63.38	45.71	109.09	63	48.57
900	77	48.88	125.88	80.50	47
1800	40	72.72	112.72	71	42.10
Threshold as a function of age	79.41	43.63	123.04	74.28	39.21

Table 6: NT-proBNP association according to the threshold 900, for the different parameters in the coronary syndrome

	NT-proBNP						**Signification Khi-deux**
	<900			**≥900**			
	Moyenne	**Ecart-type**	**Erreur standard de la moyenne**	**Moyenne**	**Ecart-type**	**Erreur standard de la moyenne**	
Age	56,7	12,9	1,9	64,3	12,1	1,8	**0.04**
Hb	13,84	1,92	,29	13,42	2,06	,32	0.61
GR	4,72	,54	,08	4,80	,53	,08	0.117
HT	40,73	5,54	,83	39,59	6,63	1,02	0.578
VGM	87,03	11,00	1,64	85,59	11,27	1,72	0.165
CCMH	35,35	8,26	1,23	33,15	5,50	,85	0.575
TCMH	32,01	3,63	,55	29,57	3,85	,59	0.010
RDW	12,8	8,1	1,2	10,0	5,8	,9	0.278
GB	10,19	5,88	,93	326,42	1944,89	315,50	0.143

CHOL	1,5392	,4761	,0710	1,5161	,3812	,0581	0.977
TG	1,645	,854	,127	1,482	,713	,109	0.361
Creat	10,04	3,07	,46	9,97	2,85	,43	0.907
Urea	,419	,255	,038	,452	,211	,032	0.117
ASAT	25,13	12,66	1,89	21,89	11,31	1,72	0.172
ALAT	20,13	10,23	1,53	19,94	12,24	1,87	0.828
Acideurique	59,68	23,49	3,50	59,90	26,28	4,01	0.822
Troponine	,1918	,2415	,0360	,5486	1,5273	,2329	0.115
HCY	15,82	6,91	1,03	20,53	22,75	3,47	0.231
FOLAT	8,26	5,59	,83	8,90	6,16	,94	0.539
VB12	355,3	146,4	21,8	349,1	214,8	32,8	0.178
NA	137,2	3,7	,5	133,2	3,2	,5	**0.000**
size	1,73	,06	,01	1,68	,06	,01	**0.021**
PDS	77,8	8,8	1,8	69,5	9,7	1,9	**0.005**
γ Gt	43,311	32,132	4,790	44,174	60,468	9,221	0.411
PAL	90,11	31,50	4,69	92,37	28,31	4,32	0.770
Bilirubine	7,365	5,537	,825	6,771	4,682	,714	0.723
K	3,96	,63	,09	3,80	,66	,10	0.163
CL	87,2	8,1	1,2	86,2	7,3	1,1	0.459
Mg	25,44	3,49	,52	23,99	5,23	,80	0.121
P	36,46	8,69	1,30	33,21	7,56	1,15	0.168
Ca	100,88	9,76	1,45	97,78	16,52	2,52	0.138
LDH	441,238	693,377	103,363	461,308	417,759	63,708	0.455
Glycemia BMI	1,293	,503	,075	1,486	,747	,114	0.343

Table 7: NT-proBNP association with different cardiovascular risk factors in coronary syndrome

	NT-proBNP class												signification
	NT-proBNP<900 NA<135			NT-proBNP≥900 NA <135			NT-proBNP<900 NA≥135			NT-proBNP≥900 NA≥135			
	Average	Standard deviation	standard error of the mean	Average	Standard deviation	standard error of the mean	Average	Standard deviation	standard error of the mean	Average	Standard deviation	standard error of the mean	
Age	55,2	15,8	3,6	65,7	13,0	2,8	58,0	10,5	2,1	63,3	11,3	2,5	**0.03**
Hb	13,96	2,75	,63	13,82	1,49	,32	13,80	1,01	,20	13,12	2,48	,57	0.437
GR	4,87	,64	,15	4,81	,61	,14	4,60	,42	,08	4,80	,46	,11	0.283
HT	40,67	7,62	1,75	41,00	6,11	1,33	40,92	3,47	,69	38,72	6,70	1,50	0.684
VGM	86,13	14,87	3,41	87,89	8,10	1,73	87,98	7,25	1,45	83,46	13,93	3,12	0.449
CCMH	37,16	12,57	2,88	33,93	1,55	,33	34,16	1,26	,25	32,08	7,96	1,83	0.789
TCMH	32,56	4,39	1,03	29,87	3,51	,75	31,51	3,03	,62	29,13	4,31	,96	0.058
RDW	13,9	9,4	2,2	9,8	4,3	,9	12,2	7,0	1,4	10,4	7,2	1,6	0.731
GB	9,86	3,60	,83	11,07	4,44	1,02	10,70	7,58	1,69	677,03	2825,8	666,0	0.498
CHOL	1,5618	,5380	,1234	1,5091	,4642	,0990	1,5298	,4431	,0886	1,5171	,2864	,0640	0.961
TG	1,638	,940	,216	1,621	,844	,180	1,667	,817	,163	1,334	,539	,121	0.585
Creat	10,33	3,44	,79	9,69	3,17	,68	9,91	2,85	,57	10,25	2,58	,58	0.960
Urea	,408	,268	,061	,468	,202	,043	,431	,254	,051	,430	,228	,051	0.374
ASAT	26,55	15,14	3,47	21,70	10,68	2,28	24,16	10,91	2,18	22,09	12,52	2,80	0.59
ALAT	18,18	8,79	2,02	18,54	11,93	2,54	21,76	11,30	2,26	22,09	12,60	2,82	0.477
Ac. urique	56,88	19,15	4,39	56,65	18,62	3,97	62,59	26,57	5,31	63,86	33,34	7,46	0.893
Troponine	,2303	,2807	,0644	,6713	2,0988	,4475	,1691	,2121	,0424	,4404	,4931	,1103	0.157
HCY	16,63	7,60	1,74	24,38	31,02	6,61	15,38	6,55	1,31	16,64	6,67	1,49	0.475
FOLAT	10,24	7,03	1,61	8,47	6,45	1,38	6,71	3,80	,76	9,13	6,04	1,35	0.504
VB12	375,2	158,0	36,2	328,5	245,5	52,4	343,2	140,9	28,2	369,3	185,1	41,4	0.301
NTproBNP	277,92	199,62	45,80	4914,45	3915,43	834,77	252,51	192,43	38,49	4535,52	6283,17	1404	**0.000**
NA	135,5	3,0	,7	132,1	3,2	,7	138,6	3,6	,7	134,4	2,9	,7	**0.000**
Size	1,74	,05	,02	1,69	,06	,02	1,72	,07	,02	1,67	,05	,02	0.111
PDS	74,3	11,3	3,6	67,0	9,1	2,3	79,6	5,2	1,4	73,2	9,8	3,1	**0.005**
Gamma Gt	43,105	29,758	6,827	35,477	30,356	6,472	44,960	34,174	6,835	52,750	82,936	18,54	0.686
Bilirubine	5,677	3,938	,903	6,651	3,542	,755	8,670	6,366	1,273	6,237	4,993	1,116	0.089
Na	131,47	1,92	,44	125,82	25,28	5,39	138,72	4,57	,91	137,20	2,14	,48	**0.000**
K	3,94	,59	,14	3,81	,76	,16	3,97	,69	,14	3,80	,58	,13	0.627
CL	86,1	9,4	2,2	86,0	8,3	1,8	88,3	7,0	1,4	86,2	6,3	1,4	0.702
Mg	26,17	2,49	,57	25,61	3,91	,83	24,95	4,11	,82	22,55	5,97	1,34	0.051
P	35,97	10,02	2,30	31,63	8,12	1,73	36,90	7,92	1,58	34,73	6,85	1,53	0.235
Ca	98,51	7,15	1,64	100,75	4,16	,89	102,92	11,23	2,25	94,75	23,73	5,31	0.052
LDH	585,842	1027,55	235,737	566,147	523,102	111,526	337,228	246,551	49,310	359,700	236,204	52,81	0.617
Glycemie	1,176	,416	,095	1,367	,674	,144	1,372	,560	,112	1,652	,812	,182	0.240

In this study, we have included 100 coronary patients with an average age 60.53 ± 12.32 years; 87.77% which are superior or equal to 50 years, with a male predominance 63.33% with a sex ratio of 1.68.

The IDM is the most commonest form in our population coronary 41.11%, 37.78% unstable angina and myocardial ischemia 21.11%, 65% are negative coronary ST.

In our patients, the most frequently associated with coronary syndrome clinical signs are chest pain and dyspnea.(Table1).

The risk factors that are associated with descending coronary syndrome are hypertension 57.77%, 48.88% smoking, dyslipidemia and diabetes 41.11% 40%.(Table2).

Hyperhomocysteinemia was present in 48.89% explained by vitamin B12 deficiency in 35.2% and a vitamin B9 deficiency in 5.2%. The average Tnhs is 0.22 ± 0.26 with extreme 0007-10 in which 58.88% of patients had an increased value to the upper value of Tnhs 0,03µg / L considered as the limit "CV <10%" of the test used. (Table1).

By considering all patients, the average of NT-proBNP is 2420.50 ± 4279 pg / ml (range 129-29096 pg / mL) in which 48.88% has a high value whatever the age and sex. The rate of NT-proBNP was associated with the Pearson correlation age, with impaired renal function. (Table3).

In our patients, NT-proBNP was also significantly related to coronary syndrome left ventricular failure compared with right ventricular failure, the coronary syndrome ST + in relation to coronary syndrome ST and the presence of dyspnea.(Table4).

The threshold of 900 pg / ml of NT-proBNP was used for laboratory diagnosis of heart failure in coronary confronts with echocardiographic signs (EF). On the threshold of 900 pg / mL according to age and sex, a very good sensitivity is obtained (77%) and a very good PPV (80.50%). Afterwards patients were first divided into two groups based on the levels of NT-proBNP (<300 and ≥300 pg / ml) whatever the age and sex and are considered as patients with a base risk and then classified according to the levels of NT-proBNP (<900 and ≥900 pg / ml) whatever the age and sex and are considered as high risk. (Table5).

45.55% of coronary patients present a rate of NT-proBNP ≥900 pg / ml whose 31.11% have a simultaneous association of high levels of troponin ehs and NT-proBNP and they are considered as high-risk patients.

The incidence of hyponatremia was 53.33% significantly associated with the levels of NT-proBNP (Table 6, 7). NT-proBNP was also significantly associated with obesity. After adjustment for other risk factors, the level of NT-proBNP is associated with advanced age, to hyponatremia and obesity.(Table6,7).

DISCUSSION

The coronary syndrome constitutes a serious cardiac disease that can evolve to a fatal and unpredictably either towards the myocardial infarction (IDM) or mortality. Meta-analysis studies have shown the diagnostic and prognostic interest of BNP and NT-proBNP in cardiovascular disease. The precision stratified risk for each individual is very important. The appearance of a rhythm disorder, sensitivity a myocardial infarction, a inflammation, a the neurohormonal activation, renal dysfunction is very important for the knowledge of this risk stra Several studies have evaluated the predictive value of NT-proBNP in the SCS.

The classification of these patients at high risk of mortalitie so that they benefit from intensive treatment such revascularization 900 ng / ml was suggested suite has its good sensitivity and good specificity compared to other thresholds. This threshold is near by 1000 ng / ml that was being used in the study of GUSTO IV (the sensitivity was 75% and the specificity was 63%. 40% have an ace Superior threshold level, they have a mortality rate of 15.3% after one year coronary syndrome compared to those with a lower rate 1000 ng / ml with a 3.4% mortality rate.[38] Doust and cal have been using meta-analysis BNP and NT-proBNP; they showed that these two markers are indicators of mortality and of myocardial infarction (IDM) patients with asymptomatic heart failure and in all cardiovascular diseases. Costello-Boerriger also postpone a meta-analysis indicating the importance of NT-proBNP as an indicator of heart failure in coronary syndrome and other pathological conditions.

In the FAST study that included elderly patients, 33% with a rate of NT-proBNP greater than 1000 ng / mL their mortality rate was 42% after 35 months of evolution compared to patients presenting a rate of lower NT-proBNP this threshold, or the mortality rate was 9% (70% sensitivity and specificité77%)[39] And finally in the study FRISC, higher than the threshold of 1000 ng / ml, the risk of mortality was 33% two years after coronary syndrome (8.6% vs. 2.5%, p <0.001).[40]

Yes NT-proBNP was significantly associated to advanced age and hyponatremia obesity .It has long been known that NT-proBNP is associated with older age and female gender. The reason that the NT-proBNP is related to the female sex is not yet clear, one of the reasons is that the prevalence of diastolic heart failure is increased in the elderly woman.[41]

The oestroprogestive used either as therapeutic pills in menopause also increases the NT-proBNP in women.[42] This hyponatremia is secondary to the increase of NT-proBNP natruiritique by his action and also to the action of vasopressin (ADH) increased following to the dilation of ventricles in the case of heart failure that accompanies coronary syndrome Hyponatremia and increase in the NT-proBNP were still considered as two markers of cardiac following response is an increase in pressure or heart volumes.[43.44.45.46.47.48] Hyponatremia always mean a sign of severity of heart failure.[49.50.51.52]

Hyponatremia and NT-proBNP as well as to advance of age predicted heart failure and mortality in coronary artery. This hyponatremia is secondary to the action of the BNP, to activation of the renin angiotensin aldosterone system, deregulation of the sympathetic nervous system, increased vasopressin.[53.54.55.56]

Our study demonstrates the negative relationship of NT-proBNP to obesity. This association was reported in the animal model in obese mouse that has a low level of NT-proBNP.[57]

Obesity may affect the BNP rate decreasing clearance of these receptors.[58.59] Obesity is a cause sometimes consequence of the decrease in NT-proBNP levels by its direct action on mitochondria at the fat cell by increasing lipolysis.[60.61] The BNP increases at the mitchondrie oxygen uptake and oxidation of fatty acids and explaining the inverse relationship between NT-proBNP and obesity.[62] The Dallas Heart Study found that the level of NT-proBNP is correlated with skeletal muscle and the adipose tissue and they postulated that the skeletal muscle decreases the synthesis or increases the elimination by androgen action in the same way that the synthesis and composition of muscle mass.[63] Cheng et al found an inverse relationship between NT-proBNP and adipose tissue vescerale indicating the role of hyperinsulinemia in the decrease in the subject obese.[64]

Other authors have confirmed the relationship between hyperinsulisme and secretion of NT-proBNP.[65.66] is possible that the NT-proBNP as a natriuretic hormone and vasodilator participate in the rupture of atherosclerotic plaque in the coronary or is thrombogenic?.

Our study confirms the diagnosis and prognostic of NT-proBNP in the coronary syndrome. in case of acute coronary syndrome or myocardial necrosis, natriuretic peptides are not secreted by the necrotic areaor ischemic because their secretion previously requires active protein synthesis chain. Although the mechanisms of elevated natriuretic peptides in acute coronary syndromes are not yet fully identified, some hypotheses involve mediators of interleukin-6 or cardiotrophin-1 in its stimulation to explain increase in situations of spontaneous or induced ischemia without necrosis detectablein particular without measurable increase in troponin. A strong association of NT-proBNP in the cardiac dyspnea in the coronary syndrome, this association was found in several studies and especially the differential diagnosis between cardiac and pulmonary dyspnea and the severity of dyspnea.

CONCLUSION

Our study confirms the association of NT-proBNP in hyponatremia, obesity and advanced age in the Coronary Syndrome. These three factors have a high mortality risk requiring further studies are in progress looking for the prognosis long-term effect of NT-proBNP on mortality or development of the IDM in the case of ischemia and unstable angina.

However this study these limits; the reduced number of the sample used in the study, there is no information on the use of diuretics in these patients to interpret hyponatremia based on taking this type of treatment still, the combination of NT-proBNP to obesity and especially on lipid metabolism as it was proved in several studies that require further studies looking for the diagnosis of heart failure in obese or obese diabetic or the general population or seeking the possibility of a new therapeutic strategy in the metabolic and particularly in heart failure.

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