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INTERRELATIONSHIP OF NT-proBNP AND ST2 CARDIAC BIOMARKERS WITH CARDIOVASCULAR FUNCTIONAL PARAMETERS UNDER CONDITIONS OF HEAD-DOWN BED REST

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Introduction. Insufficient physical activity is a key risk factors in the development of cardiovascular diseases. Such a condition can be simulated by head-down tilt bed rest (HDBR) studies, which enable the investigation of pathophysiological changes in the heart. Previous HDBR experiments have identified structural alterations in the heart, including decreased arterial pressure, impaired autonomic regulation, and vascular remodeling. However, the molecular mechanisms underlying these processes remain poorly understood.

Objective. To investigate links between functional parameters of the cardiovascular system and NT-proBNP and ST2 cardiac biomarkers.

Materials and methods. The experiment involved six volunteers who were subjected to 21-day HDBR. The parameters of heart rate variability (HRV), dispersion mapping (ECG DM), as well as levels of NT-proBNP and ST2 protein concentrations in venous blood samples, were evaluated. The examination was conducted five days before the onset of HDBR, on Days 1, 10, and 20 during HDBR, and on Day 5 after the experimental exposure. All computations were performed using the Statistica 12 statistical software package.

Results. The NT-proBNP protein concentration significantly decreased on Days 10 and 20 of the experiment, while the ST2 protein concentration was permanently decreasing from the first days of HDBR. The left ventricular depolarization index increased sharply in the middle of the study, although having returned to their baseline values by Day 5 after the cessation of the exposure. Sympathetic activity had increased by Day 20.

Conclusions. Interrelationships between functional parameters of the cardiovascular system and cardiac biomarkers were established, which may indicate that HDBR triggers the activation of neurohumoral and metabolic regulatory circuits in the setting of increased sympathetic autonomic modulating effects.

Keywords: head-down bed rest; heart rate variability; cardiac biomarkers; dispersion mapping; proteome; electrocardiogram; hypodynamia

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ВЗАИМОСВЯЗЬ КАРДИОМАРКЕРОВ NT-proBNP И ST2 С ФУНКЦИОНАЛЬНЫМИ ПАРАМЕТРАМИ СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЫ В УСЛОВИЯХ АНТИОРТОСТАТИЧЕСКОЙ ГИПОКИНЕЗИИ

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Введение. Гиподинамия является одним из ключевых факторов риска сердечно-сосудистых заболеваний. Одной из моделей изучения данного состояния является антиортостатическая гипокинезия (АНОГ), которая позволяет исследовать патофизиологические изменения в сердце. Эксперименты с АНОГ выявили структурные изменения в сердце: снижение артериального давления, нарушение вегетативной регуляции и ремоделирование сосудов. Однако молекулярные механизмы этих процессов остаются малоизученными.

Цель. Изучение связи функциональных параметров сердечно-сосудистой системы с кардиомаркерами NT-proBNP и ST2.

Материалы и методы. В эксперименте участвовали 6 испытуемых-добровольцев, которые находились в условиях 21-суточной антиортостатической гипокинезии. Проведен анализ вариабельности сердечного ритма (ВСР), дисперсионного картирования (ДК ЭКГ), а также уровня NT-proBNP и концентрации белка ST2 в образцах венозной крови. Исследования выполнены за 5 дней до начала АНОГ, на 1, 10, 20 сут в условиях АНОГ и на 5 сут после экспериментального воздействия. Все вычисления были выполнены с помощью статистического программного пакета Statistica 12.

Результаты. Было показано, что концентрация белка NT-proBNP достоверно снижалась на 10 и 20 сут эксперимента, концентрация белка ST2 уменьшалась уже с первых суток гипокинезии. Показатель деполяризации левого желудочка резко возрастал в середине исследования, но возвращался к исходным значениям к 5 сут после завершения воздействия. Симпатическая активность повышалась к 20 сут.

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Выводы. Установлены взаимосвязи между функциональными параметрами сердечно-сосудистой системы и кардиомаркерами, которые могут указывать на то, что АНОГ вызывает активацию нейрогуморального и метаболического контуров регуляции на фоне повышения симпатических вегетативных модулирующих эффектов.

Ключевые слова: антиортостатическая гипокинезия; вариабельность сердечного ритма; кардиомаркеры; дисперсионное картирование; протеом; электрокардиограмма; гиподинамия

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INTRODUCTION

Hypodynamia is currently recognized to be among the main factors negatively affecting the cardiovascular system (CVS). This condition has even been declared as a twenty-first century disease due the unequivocal connection between restricted physical activity and the etiology of atherosclerosis, arterial hypertension, coronary heart disease, and some other CVS diseases. Analysis of hypodynamia effects in patients with already developed conditions is a challenging task, since the symptoms of various pathologies can disguise the effects related to hypodynamia. In this regard, the study of hypodynamia manifestations in healthy individuals appears to be an important research direction.

Head-down tilt bed rest (HDBR) is a promising model for studying the consequences of restricted physical activity in healthy individuals (Fig. 1) [1]. This model simulates not only hypodynamia but also the fluid shift toward the head, while removing the axial load from the feet [2]. Furthermore, the gravity vector changes from the anterior to the posterior part of the body, since the volunteer remains in a supine position with the bed tilted at an angle of minus 6° for several days of HDBR exposure (Fig. 1) [3].

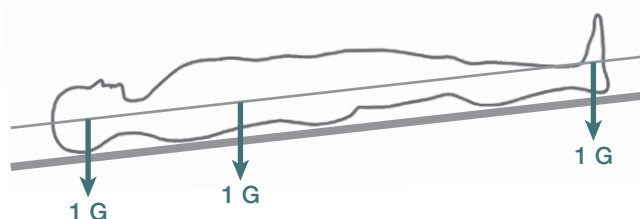


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Fig. 1. Hypodynamia model, head-down bed rest (HDBR)

HDBR studies allow changes in the CVS, primarily caused by the fluid shift in the cranial direction, to be observed [4]. Research shows that prolonged HDBR in practically healthy individuals leads to a reduction in heart chamber volumes and myocardial mass, which decreases the distensibility and functional capacity of the heart muscle [5, 6].

Chernikova et al. identified cyclic adaptive changes in CVS function during a 120-day HDBR period. Specifically, the initial stages of the experiment demonstrated a decrease in baroreflex function, a reduction in systolic arterial pressure and heart rate (HR), as well as a predominance of sympathetic influences and a weakening of the autonomous circuit of autonomic regulation¹. Under conditions of hypokinesia, chronic unloading led to remodeling of the arterial system in the legs, associated with atrophy of vascular smooth muscle. In independent studies by Palombo et al. and Platts et al., a 21-day HDBR exposure resulted in a decrease in the diastolic volume and mass of the left ventricle, as well as changes in hemodynamics and an increase in aortic stiffness [7, 8].

The HDBR influence on the morphofunctional parameters of the CVS has been comprehensively described in literature. However, the molecular mechanisms underlying these changes remain poorly understood. Such studies are particularly relevant for the development of personalized medicine approaches, since it is molecular processes that form the basis of the body's individual adaptive responses.

Cardiovascular proteomics is a promising research direction which addresses the interactions of proteins regulating the CVS function. Understanding these processes is extremely important in view of the role of autonomic and metabolic mechanisms in the body's adaptation to changing conditions, including hypodynamia. Particular attention is paid to cardiac biomarkers, such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and soluble suppression of tumorigenicity 2 (sST2),

¹ Chernikova AG. Assessment of the functional state of the body during long-term space flight based on heart rate variability analysis: abstract [dissertation]. M.: Inst. Med.-Biol. Probl.; 2010

which allow CVS dysfunction to be detected at the molecular level. These markers are capable of reflecting hidden changes preceding clinical manifestations, thus possessing high diagnostic value [9].

The sST2 soluble growth stimulation factor is expressed in cardiac tissue in response to pathological changes induced by both chronic diseases and acute injuries, manifesting the processes of ventricular remodeling and cardiac fibrosis. The NT-proBNP biomarker allows chronic obstructive pulmonary disease to be distinguished from chronic heart failure. Previous studies have established that the levels of these cardiac biomarkers change under conditions of spaceflight and parabolic flight. Changes in their levels were observed both during and after the exposure; however, within a few days, the indicators returned to their baseline values [9, 10].

Adaptive responses of the body are largely determined by nonlinear dynamic processes, including heart rate variability (HRV). Heart rate variability forms under the influence of autonomic regulation of the sinoatrial node (SA node), the bioelectrical activity of the heart generated by heart-brain interactions, and dynamic nonlinear processes of the autonomic nervous system [11]. From a physiological standpoint, HRV is an integral characteristic reflecting not only the response of cardiac structures and the CVS as a whole to external influences, but also the response of more complex neural networks at different levels of the CNS [12].

In this study, we aim to investigate a potential relationship between the functional parameters of CVS and the proBNP and ST2 cardiac biomarkers under conditions of HDBR.

MATERIALS AND METHODS

Six practically healthy male volunteers (age range 24–40 years, BMI 23.8 ± 2.7 kg/m²) were invited to

participate in a 21-day HDBR experiment [13] to simulate hypodynamia and analyze its effects.

The experiment was conducted at the Institute of Biomedical Problems of the Russian Academy of Sciences (IBMP RAS) using the Hypogravity test facility.

During the experimental exposure, electrocardiogram (ECG) recording and venous blood collection were performed on Days 1, 10, and 20 of HDBR. Baseline studies were conducted prior to and following the experiment, namely five days before the onset of HDBR and on Day 5 after the experimental exposure.

To assess bioelectrical processes in the myocardium, ECG was recorded in two standard leads over 24 h, followed by an analysis of HRV and dispersion mapping (ECG DM), which characterize the electrophysiological properties of the myocardium. The following standard HRV parameters were assessed: the standard deviation of all normal-to-normal intervals SDNN (ms) and the power spectral density in the low-frequency range LF (ms²). In addition, parameters characterizing bioelectrical stability/instability in the myocardium, including the dispersion characteristic of the PQRST complex on the ECG during the completion of left ventricular depolarization (G4) [14].

Venous blood sampling was performed in the morning in a fasting state. The level of NT-proBNP was measured using a Finecare FIA FS-113 immunoassay analyzer (Guangzhou Wondfo Biotech, China). The concentration of the ST2 protein was determined by enzyme-linked immunosorbent assay (ELISA) using a commercial Aspect Plus Kit (Critical Diagnostics, USA), with a minimum detection limit of 12.5 ng/mL [15].

Since the majority of the studied sample distributions failed to meet the normality criteria according to the Jarque–Bera test, the Spearman's rank correlation coefficient (r_s) was also applied with an assessment of the significance level (p) [16]. All calculations were

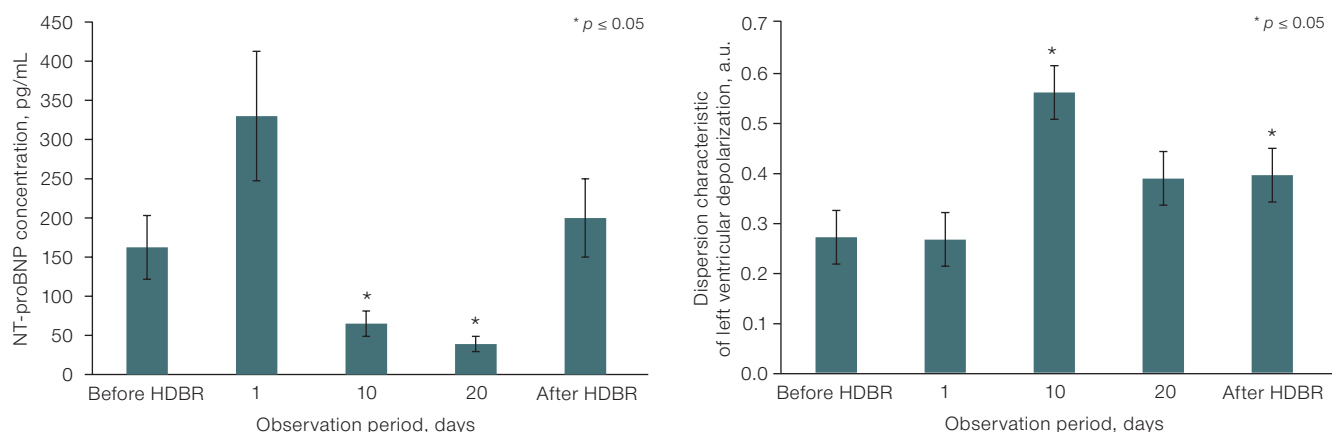


Figure prepared by the authors based on original data

Fig. 2. Dynamics of the dispersion mapping parameter and NT-proBNP protein before, during, and after head-down bed rest (HDBR)

performed using the Statistica 12 statistical software package (StatSoft, USA).

RESULTS

During the study, the dynamics of the NT-proBNP protein change were assessed in six healthy male volunteers throughout the entire research period. A significant decrease in its concentration was observed on Days 10 and 20 of the exposure compared to the baseline levels (102.6 ± 65.4 pg/mL). This may indicate a reduction in circulating blood volume by the middle of the experiment. The corresponding data are presented in Figure 2.

The values of the G4 index, reflecting the process of left ventricular depolarization, on Days 10 and 20 of HDBR increased almost threefold (to 0.6 a.u.) compared to the baseline values (0.2 a.u.). However, by Day 5 of the recovery period, the index value had corresponded to the initial (baseline) levels ($p \leq 0.05$).

The ST2 protein concentration in the volunteers ranged 21.4 ± 2.7 ng/mL five days before the onset of the experiment and was significantly decreasing ($p \leq 0.05$) starting from Day 1 of the exposure. The corresponding data are presented in Figure 3.

The SDNN index is one of the most informative HRV parameters, which reflects autonomic modulation in the SA node. It increased on Day 1 of HDBR, then gradually decreasing on Days 10 and 20 of the experiment.

The increased activity of the sympathetic division of autonomic regulation during the experiment in all subjects is illustrated in Figure 2. The low-frequency component of the HRV spectrum (LF, ms^2), which characterizes the dominance of sympathetic effects on heart rhythm, increased both on Day 20 of the HDBR exposure and during the recovery period, which may indicate the development of fatigue and stress during the final stages of the experiment.

It is worth noting that the changes in the dynamics of the ST2 protein and the LF (ms^2) index were inversely proportional.

When analyzing the results obtained using Spearman's rank correlation criterion, a relationship between CVS parameters and cardiac biomarkers was established (Table). These data show that before the HDBR exposure, the correlations between most parameters were weak and statistically insignificant. The levels of NT-proBNP and ST2 proteins showed a significant correlation with CVS parameters on Days 10 and 20 of the exposure, which likely reflects the processes of myocardial adaptation and recovery.

DISCUSSION

The BNP protein, being a heart failure marker, is capable of reducing the load on the heart. This protein dilates blood vessels, suppresses the renin and aldosterone production, improves collateral blood flow in the heart,

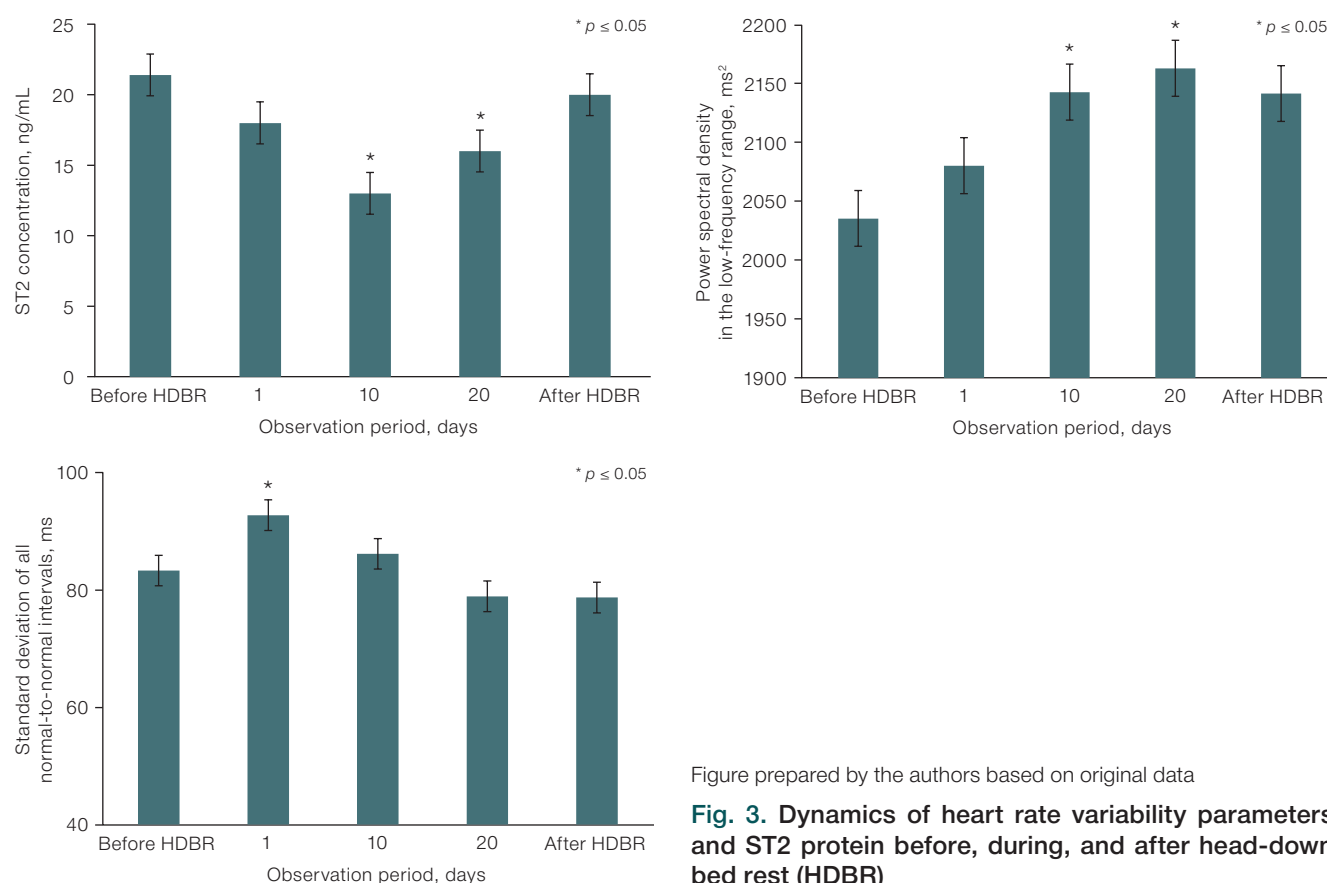


Figure prepared by the authors based on original data

Fig. 3. Dynamics of heart rate variability parameters and ST2 protein before, during, and after head-down bed rest (HDBR)

Table. Correlations between NT-proBNP and ST2 cardiac biomarkers and parameters of heart rate variability and dispersion mapping, identified in the study

Protein	Cardiovascular system (CVS) parameter	Observation duration, days				
		before HDBR	1	10	20	after HDBR
NT-proBNP	Dispersion characteristic of left ventricular depolarization, a.u.	0.26	0.45	-0.91*	-0.88*	-0.35
ST2	Standard deviation of all normal-to-normal intervals, ms	0.41	0.88*	0.64*	0.43	0.48
	Power spectral density in the low-frequency range, ms ²	-0.34	0.55	-0.88*	-0.74*	-0.26

Table compiled by the authors based on original data

Note: NT-proBNP — N-terminal pro-brain natriuretic peptide; ST2 — suppression of tumorigenicity 2; HDBR — head-down bed rest; the table contains the values of Spearman's rank correlation coefficient. (r_s); * — $p \leq 0.05$.

and reduces the load on the myocardium. As a result, a decrease in heart rate and blood pressure is observed, cardiac and vascular remodeling is reduced, and the risk of hypertrophy and thickening of the myocardial walls is lowered. It is known that the level of NT-proBNP largely depends on a set of various factors, such as circulating blood volume, changes in renal hemodynamics, and others [17].

Already on Day 1 of human exposure to HDBR conditions, a shift of body fluid components in the cranial direction was observed. On subsequent days, a gradual increase in heart rate in the setting of decreasing blood NT-proBNP concentration was noted. However, during the recovery period, the NT-proBNP level increased by almost 150 pg/mL compared to the values on Day 20 of HDBR, which likely indicates the reinclusion of gravitational load. A similar dynamic in NT-proBNP levels was recorded in other studies, particularly on Day 4 of recovery after a 7-day dry immersion [18], confirming the role of re-adaptation to orthostatic conditions in activating the natriuretic peptide response.

According to a number of studies, an increase in electrical and ion-metabolic instability is directly related to an increase in overall HRV and its parasympathetic component [19]. The electrical activity of the right atrium is largely determined by the activity of the SA node located there. Consequently, fluctuations in the ECG DM parameter may reflect processes of sinus arrhythmia in cardiac activity. Furthermore, fluctuations in venous return to the heart and changes in hemodynamic load on the atria can also lead to increased electrical instability in the atria. Regardless of the initial health status, with relatively preserved autonomous mechanisms of cardiac regulation in humans, activation of parasympathetic modulating influences on heart rhythm can lead to stabilization of the heart electrical activity, manifested as a decrease in dispersion parameters. Under

a pronounced deficit in parasympathetic modulation reserves, an impairment of atrial depolarization processes is observed, manifested by an increase in the ECG DM parameter [19].

The correlation between the NT-proBNP level and ECG DM indices identified in our study has a physiological basis. Thus, it was previously shown that during atrial fibrillation (AF), the levels of natriuretic peptide [20, 21], as well as the NT-proBNP to BNP ratio [22], increased. Rapid AF with its variable cycle length and ventricular filling time can lead to chaotic micro-regional changes in the deformation of atrial cardiomyocytes, potentially distorting and stretching local cardiomyocyte populations, causing the release of pro-BNP in the absence of increased mean intracardiac or transmural stretch pressure. Histological examination of atrial tissue in AF revealed inflammatory, hypertrophic, and fibrotic changes that could have contributed to increased expression and release of pro-BNP. These findings are consistent with the identified increased content of pro-BNP RNA messenger in atrial tissue. Together, these effects elevated the pro-BNP plasma level in AF [21].

Ozmen et al., when investigating the relationship between NT-proBNP and the frequency and severity of ventricular arrhythmia, found that NT-proBNP levels were significantly higher in the malignant arrhythmia group (Lown Class 4a and 4b arrhythmia) compared to the benign arrhythmia group (Lown Class 0–3b arrhythmia) [23].

All these studies indicate the existence of a relationship between myocardial distensibility, reflected by the NT-proBNP marker, and the rhythm of myocardial contractions (depolarization of the right atrium and left ventricle).

One possible mechanism contributing to the reduction of ventricular mass and decreased stretching of cardiomyocytes may be the interrelationship between

a potential stabilizing effect on the left ventricular end-diastolic volume and a simultaneous increase in its end-systolic volume, observed under the conditions of reduced loading during HDBR. Activation of sympathetic nerves leads to vasoconstriction of blood vessels in most organs, increased myocardial contractility, and, through its influence on the SA node, to tachycardia. It seems possible that the decrease in ST2 in the middle and at the end of the experiment activates sympathetic autonomic modulations, which, in turn, affects heart rhythm.

Furthermore, the predominance of the low-frequency component in the overall HRV spectrum may indicate an intensification of neurohumoral regulation, as well as increased activity of the vasomotor center [24]. At the same time, prolonged sympathetic stimulation of cardiac activity is accompanied by the activation of metabolic processes in the myocardium, leading to

a significant increase in oxygen and energy resource consumption [25].

CONCLUSION

In this study, we examined the dynamics of functional parameters of the CVS under conditions of HDBR, with a particular focus on molecular biochemical markers of cardiac dysfunction — proBNP and ST2. Our research has revealed an interrelationship between the functional parameters of the cardiovascular system and the proBNP and ST2 cardiac biomarkers. Under conditions of head-down bed rest, activation of neurohumoral and metabolic regulatory circuits occurs in the setting of increased sympathetic autonomic modulating effects. At the same time, the remodeling processes taking place in the heart muscle at the cardiomyocyte level are caused by an increase in their distensibility.

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