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Forum Review

Effects of Intermittent Hypoxia on the Heart

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ABSTRACT

Obstructive sleep apnea (OSA) is associated with cardiovascular diseases such as hypertension through mechanisms involving intermittent hypoxia (IH). However, it is not yet clear whether IH directly affects the heart. In a mouse model of OSA, we found that IH causes time-dependent alterations of the susceptibility of the heart to oxidative stress. Acute IH can exert preconditioning-like cardioprotection, in part, through the transcriptional activation of genes such as *bcl-x*$_L$ and *gata4*. We cloned the mouse *gata4* promoter and identified an IH-responsive region. The exposure of mice to prolonged IH results in the increased susceptibility of the heart to ischemia–reperfusion injury by increasing the oxidative stress status. This might resemble conditions of OSA patients. In our mouse model, further exposure to prolonged IH allowed reversal of the enhancement of myocardial damage. Understanding the complex effects of IH on the heart should help ultimately to develop therapeutic strategies against OSA-induced complications. *Antioxid. Redox Signal.* 9, 723–729.

OBSTRUCTIVE SLEEP APNEA AND CARDIOVASCULAR DISEASES

Obstructive sleep apnea (OSA) is a symptomatic sleep-disordered breathing condition characterized by the occurrence of repetitive episodes of airflow obstruction during sleep with persistent efforts to breathe (32). OSA syndrome is often indicated by loud snoring, breathing pauses, feeling of nonrefreshing sleep, and excessive daytime sleepiness. It has been reported that 24% of North American men and 9% of women have more than five apneic/hypopneic events per hour of sleep (72). The prevalence of OSA with more than five apneic/hypopneic events per hour and daytime sleepiness was reported to be 4% in male and 2% in female subjects (72).

In addition to daytime sleepiness, impaired cognitive performance, and behavioral changes, OSA is considered to be a risk factor for cardiovascular disorders, with life-threatening consequences. These cardiovascular diseases include systemic hypertension (28, 38, 43), pulmonary hypertension (50), myocardial infarction (22, 49), atherosclerosis (41, 51), stroke (2, 17), heart failure (52), and cardiac arrhythmias (47, 48, 53). Mechanisms by which sleep-disordered breathing affects the cardiovascular system, however, have not been defined.

Heart failure in OSA patients could occur because of the increased susceptibility of the heart to ischemic injury or failing of the dilated heart subsequent to pressure overload–induced cardiac hypertrophy in conditions such as systemic hypertension and pulmonary hypertension (36, 45, 46, 54, 56). OSA has been shown to affect myocardial ischemia (9, 29, 42, 51, 64). Apnea index was found to be an independent predictor of myocardial infarction after adjusting for age, body mass index, hypertension, smoking, and cholesterol level (22). Franklin *et al.* (19) reported that hypoxemia might induce nocturnal angina.

Continuous positive airway pressure (CPAP) has been used to treat OSA patients. This therapy is effective in reducing daytime sleepiness. However, patients receiving CPAP therapy still experience some apneic episodes (16), and many patients discontinue use of CPAP because of inconvenience or intolerance (18). Because of incomplete effectiveness and inconsistent use, long-term consequences of OSA on the cardiovascular system may not be eliminated by CPAP. Thus,

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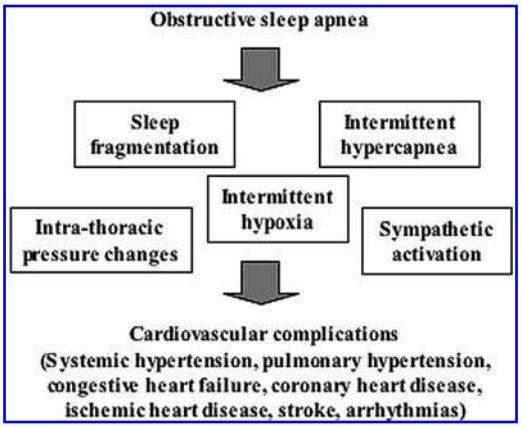

FIG. 1. Possible mechanisms for OSA-induced cardiovascular complications.

further understanding of the effects of OSA on the cardiovascular system is needed to provide optimal strategies to reduce the risk of cardiovascular diseases associated with OSA.

OSA may alter the cardiovascular system by mechanisms involving (a) intermittent hypoxia (IH), (b) intermittent hypercapnea, (c) intrathoracic pressure changes, (d) sympathetic activation, and (e) sleep fragmentation (27) (Fig. 1). OSA patients experience IH with repeated episodes of hypoxia (lasting from 10 sec to 2 min) and normoxia during sleep. Reoxygenation subsequent to hypoxia may produce reactive oxygen species (ROS) (12, 27, 44, 62). Inflammatory responses (11) as well as increased sympathetic tone and elevated catecholamine (55) also may increase the ROS production in OSA patients. ROS can oxidize biologic molecules, including lipids, proteins, and DNA, and can inhibit biologic functions (57). ROS also serve as mediators of signal transduction, which plays critical roles in the development of cardiovascular diseases (58, 59, 61).

IH AND THE HEART

IH with repeated episodes of hypoxia and reoxygenation, which occur in OSA patients, resembles repeated brief episodes of ischemia and reperfusion, which cause ischemic preconditioning. Ischemic preconditioning is a powerful form of endogenous protection against myocardial infarction (66). Murry *et al*. (34) originally demonstrated that four cycles of 5-min ischemia and 5-min reperfusion reduced infarct size induced by subsequent prolonged ischemia in a dog model. Similarly, patients who have angina shortly before a heart attack have smaller infarcts than do patients without prior angina (termed "warm-up phenomenon") (23).

Consistently, IH was found to exert cardioprotection in humans and animal models (Table 1). In humans, a hypobaric IH protocol was used to treat patients with coronary heart disease and dyslipidemia. After 10 months, in none of 37 patients did myocardial infarction develop (65). Burtscher *et al.* (6) reported that 15 sessions of IH with three to five cycles of 10–14% O_2 (3–5 min) plus 21% O_2 (3 min) over a 3-week period increased exercise tolerance in elderly men with and without coronary artery disease.

Similar to the observations in humans, IH was found to protect the heart in animals. IH with five to eight episodes of 10% O_2 (5–10 min) plus 21% O_2 (4 min) protected canine myocardium from infarction (75). Cai *et al*. (7) reported that treatment of mice with five cycles of 6-min 6% O_2 + 6-min 21% O_2 protected the heart against subsequent ischemia–reperfusion injury. This protection was not detected in hypoxia-inducible factor-1 (HIF-1) knockout mice, suggesting the role of HIF-1. Authors also concluded that the protective mechanism induced by IH is different from that promoted by ischemic preconditioning. Whereas ischemic preconditioning induces both early and delayed phases of protection, IH activates only the delayed protective mechanism. Further, IH increased the expression of erythropoietin in the kidney, but no alterations in gene expression were noted in the heart (7). Zhou *et al*. (73) reported that placing rats in a hypobaric chamber for 6 h/day for 4–6 weeks altered levels of antioxidants (73), heat-shock protein 70 (74), ATP-dependent potassium channels (76), pro- and antiapoptotic proteins (15), protein kinase C (13), inducible nitric oxide synthase (14), and calcium regulatory proteins (68, 70, 71).

Recently, Beguin *et al*. (3) reported that rats treated with short-term IH with cycles of 40-sec 10% O_2 + 20-sec 21% O_2 for 4 h had reduced myocardial infarction induced by subsequent ischemia–reperfusion. Signal-transduction pathways activated in response to short-term IH in the heart have not been identified. We found that the treatment of mice with short-term IH in an OxyCycler Oxygen Profiling Chamber (BioSpherix, Redfield, NY) (Fig. 2A) with five cycles of 2 min 10% O_2 + 2-min 21% O_2 (Fig. 2B), which might mimic the condition of human OSA, induced the mRNA expression of antiapoptotic *bcl-*x_L in the heart (39). The promoter region

TABLE 1. SUMMARY OF THE STUDIES OF IH ON THE HEART

Species	*IH protocol*	*Cardiac effects*	*Ref.*
Humans	Three to five cycles of 3- to 5-min 10–14% O_2 + 3-min 21% O_2 (15 sessions over 21 days)	Protective	6
Dogs	Five to eight cycles of 5- to 10-min 10% O_2 + 4-min 21% O_2 (one session per day for 20 days)	Protective	75
Rats	240 cycles of 40-sec 10% O_2 + 20-sec 21% O_2 (one session)	Protective	3
Rats	240 cycles of 40-sec 5% O_2 + 20-sec 21% O_2 (one session)	Damaging	3
Rats	480 cycles of 40-sec 5% O_2 + 20-sec 21% O_2 (one session per day for 35 days)	Damaging	24
Mice	Five cycles of 6-min 6% O_2 + 6-min 21% O_2 (one session)	Protective	7
Mice	120 cycles of 2-min 6% O_2 + 2-min 21% O_2 (one session per day for 7–14 days)	Damaging	40

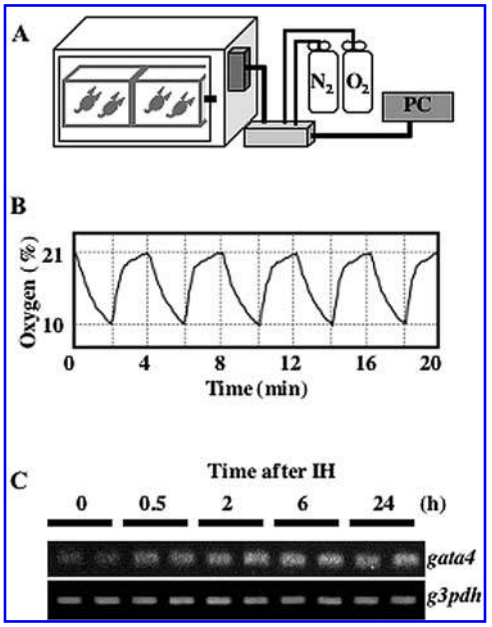

FIG. 2. Experimental protocol to elicit acute intermittent hypoxia. (**A**) Schematics of experimental settings in our laboratory. Mouse cages are placed in a chamber connected to the OxyCycler Oxygen Profiler, which controls O_2 levels. (**B**) The O_2 level is set to be altered from 21% to 10% in 2 min, and then back to 21% in 2 min. The actual changes in O_2 levels are shown. (**C**) Mice were subjected to IH with five cycles of 2-min hypoxia (10% O_2) plus 2-min normoxia (21% O_2) and maintained in the normoxic condition for durations indicated. Total RNA was isolated from left and right ventricles and analyzed by reverse transcription–polymerase chain reaction by using primers for mouse *gata4* or *g3pdh* mRNA. Adopted from Park *et al.* (39).

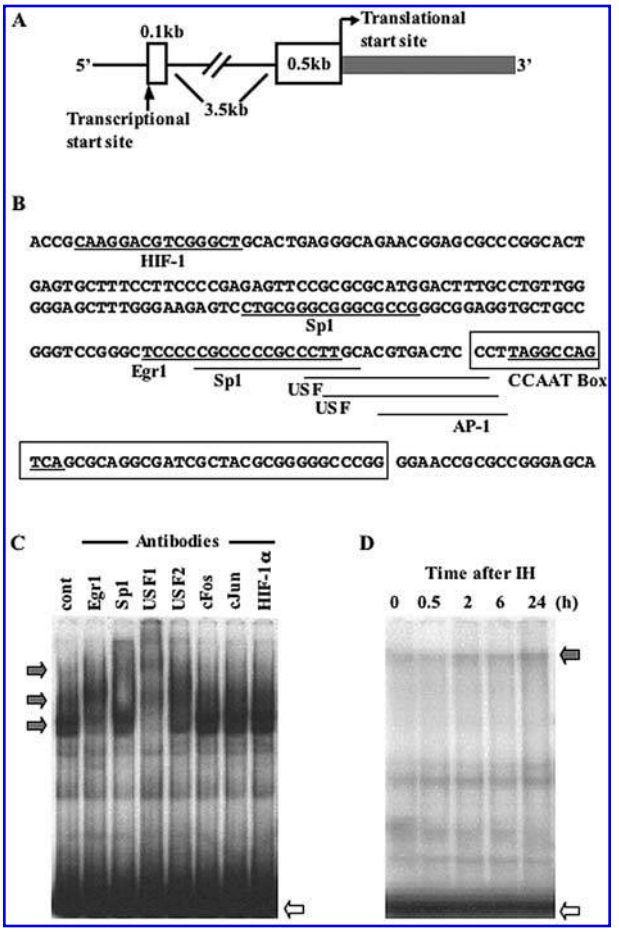

FIG. 3. Structure of mouse *gata4* gene. (**A**) A scheme depicting the mouse *gata4* gene structure with the major transcriptional start site of mouse *gata4* gene that was identified by 5′RACE to occur ~4 kb upstream of the translational start site. (**B**) Sequence of the 250-bp region immediately upstream from the transcriptional start site. Putative transcription factor binding sites are indicated. The region marked with *rectangles* is the sequence of band-shift probe used for experiments in Fig. 4D. (**C**) HL-1 adult mouse cardiac muscle cell nuclear extracts were subjected to electrophoretic mobility-shift assay with the ^{32}P-labeled 250-bp region, and transcriptional binding factors were identified with various antibodies in supershift experiments. *Solid arrows*, Major bands noted in the absence of antibodies. *Open arrow*, The free probe. (**D**) Mice were subjected to IH with five cycles of 2-min hypoxia (10% O_2) plus 2-min normoxia (21% O_2) and then maintained in the normoxic condition for durations indicated. Nuclear extracts were subjected to electrophoretic mobility-shift assay by using a ^{32}P-labeled double-stranded oligonucleotide containing the sequence in the rectangle in Fig. 4B. *Solid arrow*, The band that was increased in response to acute IH. *Open arrow*, The free probe. Adopted from Park et al. (39).

of the *bcl-x* gene, which controls the expression of the anti-apoptotic isoform Bcl-x_L, contains two important GATA-binding elements (1, 25). IH was found to activate the GATA-4 DNA-binding activity as well as *gata4* mRNA expression (Fig. 2C; 39). These results suggest that IH might promote gene transcription of *bcl-x_L* through the activation of GATA-4 that occurs in response to increased *gata4* gene transcription.

To determine the mechanism of *gata4* gene transcription, we examined the effects of short-term IH on the *gata4* gene promoter (35, 39). We first performed 5′ Rapid Amplification of cDNA Ends (RACE) analysis to identify the transcriptional start region within the *gata4* gene. 5′RACE using mouse ventricular RNA revealed the 5′ end of *gata4* mRNA to be 0.6 kb upstream from the ATG start codon. The analysis of the *gata4* genomic DNA sequence further suggested that the transcriptional start site is 4.1 kb upstream of the ATG translational start site. This 4.1-kb genomic region contains a 3.5-kb intron, which is present 0.1 kb downstream from the transcriptional start site (Fig. 3A).

The 1-kb 5′ flanking region immediately upstream from the transcriptional start site promoted the luciferase reporter expression in transfected cardiac muscle cells. This region shares 90% homology with the rat *gata4* gene and contains putative binding sites for various transcription factors. Truncation of a 1-kb to 500- or 250-bp fragment did not attenuate the promoter activity, suggesting that the 250-bp region immediately upstream from the transcriptional start site contains important regulatory elements for basal expression of GATA-4. The 250-bp proximal region contains binding sites for early growth response 1 (Egr1), specificity protein 1 (Sp1), upstream stimulating factor (USF), activator protein-1 (AP-1), and HIF-1, as well as a CCAAT box (Fig. 3B). Supershift

experiments using antibodies against Egr1, Sp1, USF1, and USF2 demonstrate the binding of these factors to the proximal 250-bp fragment (Fig. 3C). No alterations of the binding characteristics were detected with antibodies against cFos/cJun/AP-1 or HIF-1α. We found that a yet-unidentified transcription factor, which binds to the CCAAT box, is activated in response to short-term IH (Fig. 3D; 39).

The promotion of gene transcription may involve acetylation of various transcriptional regulatory proteins. Nuclear protein acetylation is regulated by histone acetyltransferase and histone deacetylase (HDAC) (10). Indeed, we found that acute IH promoted lysine acetylation of various nuclear proteins in the mouse heart. We hypothesized that IH might influence the activity of HDAC, which in turn affects the acetylation state of transcriptional regulators for cardioprotective signaling. To define the mechanism of the promotion of gene transcription induced by IH, the total HDAC activity was measured in heart nuclear extracts from mice subjected to IH (five cycles of 2-min 10% O_2 + 2-min 21% O_2). Interestingly, we found that IH transiently inhibited the nuclear HDAC activity. These results support the hypothesis that IH reduces the HDAC activity in the nucleus, resulting in the promotion of nuclear protein acetylation. Acetylation of the transcriptional regulatory apparatus may then increase gene transcription of *gata4*, perhaps via the regulation of CCAAT box (Fig. 4). Further, lysine acetylation of GATA-4 may block the ubiquitin-mediated degradation, thus enhancing GATA-dependent biologic activities (60).

The clinical significance of the ability of IH to exert cardioprotective effects in OSA patients is still unclear, especially because data on the effects of apnea on cardioprotective signaling in the hearts of OSA patients are not available. Understanding the mechanisms of the effects of IH in a mouse model of OSA should provide important information, which may ultimately result in therapeutic strategies to prevent and/or treat OSA-induced complications.

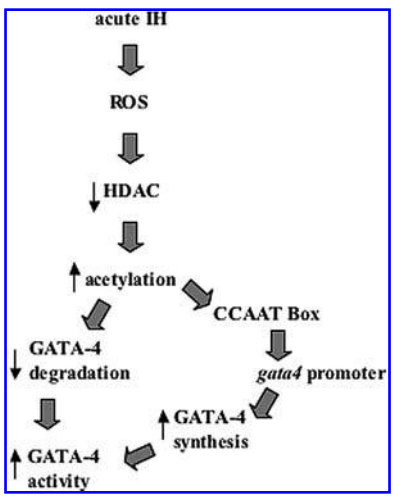

FIG. 4. Hypothetical mechanism for acute IH-mediated alterations of GATA-4–dependent gene transcriptional regulation via inhibition of HDAC. We hypothesize that acute IH produces ROS, which in turn inhibit HDAC, promoting protein acetylation. The GATA-4 molecule can be acetylated (60), and this may in turn inhibit the ubiquitin-mediated degradation of GATA-4. Acetylation of histones and transcription factors may also promote transcription of the *gata4* gene, perhaps via CCAAT box, and increase GATA-4 synthesis.

IH AND INCREASED SUSCEPTIBILITY OF THE HEART TO OXIDATIVE STRESS

It should be noted that, in contrast to effects of IH to exert cardioprotection, some studies also demonstrated that IH enhanced ischemia–reperfusion damage. In the study by Beguin *et al*. (3), rats treated with cycles of 40-s 10% O_2 + 20-s 21% O_2 for 4 h had reduced myocardial infarction induced by ischemia–reperfusion; however, changing the O_2 levels during the hypoxic phase to 5% increased the infarct size. Joyeux-Faure *et al.* (24) reported that long-term IH (40-s 5% O_2 + 20-s 21% O_2, 8 h/day for 35 days) enhanced ischemia–reperfusion-induced myocardial infarction in the rat heart. This might resemble observations in humans that OSA is associated with increased myocardial infarction (49, 52). Thus, IH can increase or decrease the susceptibility of the heart to ischemia–reperfusion stress, depending on the time course and intensity of hypoxia.

ADAPTATION OF THE HEART TO IH

Our studies showed that prolonged IH (2-min 6% O_2 + 2-min 21% O_2, 8 h/day for 1–2 weeks) exaggerated myocardial ischemia–reperfusion injury in C57BL/6 mice (40). Interestingly, however, hearts from mice exposed to 4 weeks of IH had ischemia–reperfusion-induced myocardial injury levels similar to those in control hearts of normoxic mice. These results suggest that 1–2 weeks of IH increased the susceptibility of the heart to ischemia–reperfusion injury, whereas the heart appears to adapt to IH by 4 weeks by normalizing the susceptibility to oxidative stress (Fig. 5).

Ischemia–reperfusion-induced lipid and protein oxidation was enhanced with 1–2 weeks of IH. With 4 weeks of IH, the

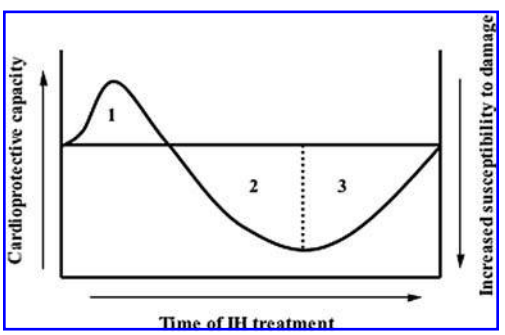

FIG. 5. Time-dependent effects of IH on susceptibility of the heart to oxidative stress. Experiments from our laboratory and others showed that IH can exert three effects on myocardial ischemia–reperfusion injury: (a) short-term IH treatment protects the heart against ischemia–reperfusion injury; (b) prolonged IH treatment enhances ischemia–reperfusion injury; and (c) the heart can adapt to IH enhancement of ischemia–reperfusion injury.

level of oxidative stress was normalized to the level in animals without IH treatment (40). Thus, IH-mediated changes in the susceptibility of the heart to ischemia–reperfusion injury are dependent on oxidative stress.

A mouse model of OSA provided important information that long-term IH can dynamically alter the susceptibility of the heart to oxidative stress. Further understanding of these events might reveal the mechanism of the individual differences among OSA patients in cardiovascular diseases development.

CHRONIC SUSTAINED HYPOXIA AND CARDIOPROTECTION

Hearts of chronically hypoxic animals also develop reduced levels of myocardial infarction in response to ischemic insult (31, 67) and exhibit better functional recovery (30, 63, 69). The protection against ischemia–reperfusion by chronic hypoxia can last longer than any other forms of preconditioning (26). Further, cardioprotection by hypoxic and ischemic preconditioning is not additive (37); and the degrees of myocardial tolerance to prolonged and intermittent hypoxia treatments are different (33). Chronic hypoxia can induce pulmonary hypertension, and myocardial ischemia may occur during heart failure in patients with pulmonary hypertension (4, 5, 8, 20, 21). Thus, understanding the relation between chronic hypoxia and cardioprotection may help to develop therapeutic strategies against pulmonary hypertension and right heart failure.

CONCLUDING REMARKS

Heart failure as a consequence of ischemia–reperfusion injury is the leading cause of death in the United States and other Western countries. Hypoxic respiratory disorders such as OSA have been recognized as an important risk factor for cardiovascular diseases. Heart failure in OSA patients may occur because of the increased susceptibility of the heart to ischemic injury and myocardial infarction. The heart possesses effective endogenous cardioprotective mechanisms such as ischemic preconditioning, in which the heart is subjected to repeated episodes of mild ischemia and reperfusion. The susceptibility of the heart to ischemia–reperfusion injury and other types of oxidative stress is altered by various pathophysiologic and environmental conditions including IH. Understanding the mechanisms of how IH influences endogenous cardioprotective events and the susceptibility of the heart to oxidative stress should be useful for designing therapeutic strategies to reduce heart failure.

In mice, IH can exert time-dependent, triphasic effects on cardioprotective signaling: (a) the initial preconditioning-like protective event; (b) followed by the increased susceptibility to ischemia–reperfusion injury; and (c) adaptation and normalization of the susceptibility to ischemia/reperfusion injury (Fig. 5). In response to short-term IH, the expression of cardioprotective genes such as *bcl-x*$_L$ and *gata4* can be promoted. We identified a short-term–IH-responsive region within the *gata4* promoter. Prolonged IH treatment for 1–2 weeks can increase the susceptibility of the heart to ischemia–reperfusion injury, and this can be normalized with 4 weeks of IH in our mouse model. Changes in the susceptibility of the heart to ischemia–reperfusion injury are associated with similar trends, which occur in lipid and protein oxidation profiles, suggesting the involvement of ROS. Further understanding of preconditioning-like actions of short-term IH and adaptive mechanisms in response to prolonged IH should help to reveal the mechanisms of endogenous cardioprotection.

ACKNOWLEDGMENT

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ABBREVIATIONS

AP-1, activator protein-1; CPAP, continuous positive airway pressure; Egr1, early growth response 1; HDAC, histone deacetylase; HIF, hypoxia inducible factor; IH, intermittent hypoxia; LDH, lactate dehydrogenase; OSA, obstructive sleep apnea; ROS, reactive oxygen species; Sp1, specificity protein 1; USF, upstream stimulating factor.

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