Original Article

Sevoflurane improves contractile function in stunned myocardium through KATP channels in dogs

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Abstract

This investigation examined the role of myocardial adenosine triphosphate-regulated potassium (KATP) channels in sevoflurane-induced myocardial protection of stunned myocardium in dogs. Stunned myocardium was produced by occluding the left anterior descending artery (LAD) 5 times for 5 min each, interspersed with 5 min periods of reperfusion before prolonged LAD occlusion. Dogs (n=22) were instrumented for measurement of heart rate (HR), left ventricular (LV) and aortic blood pressure (AP), cardiac output (CO), maximum rate of increase of LV pressure (LVdp/dt max) and percent segment shortening (%SS). Dogs were divided into 3 groups : Group C, control group (n=7) ; Group S, sevoflurane 1-minimum alveolar anesthetic concentration (MAC) anesthesia for 75 min before and after stunning (n=7) ; and Group G, pretreated with glyburide before sevoflurane anesthesia (n=8). Hemodynamic and metabolic variables and LV function were measured in the basal anesthetic state (baseline), at sevoflurane anesthesia for 30 min (S-30), after stunning (before reperfusion ; BR), and at 5 intervals after reperfusion of LAD occlusion. Regarding regional dyskinesia, although there was no significant differences between groups, Group S demonstrated better recovery of %SS than Group C and G in comparison with each baselines. Group G displayed sustained systolic dysfunction after 180 min reperfusion. Sevoflurane-induced cardioprotective effects were associated with the microscopic differences in myocardial tissue among groups. Sevoflurane enhances recovery of myocardial contractile function, and these effects are blocked by glyburide pretreatment.

(Key words : sevoflurane ; KATP channel ; stunned myocardium)

Introduction

Myocardial stunning is a ischemia-reperfusion injury described as a prolonged postischemic

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ventricular dysfunction. Volatile anesthetics exert cardioprotective effect through improving recovery of contractile function of stunned myocardium. Ischemic preconditioning (IPC) is a phenomenon defined as brief periods of ischemia have been shown to protect the myocardium against a prolonged ischemia. Animal experiments indicate volatile anesthetics have a strong preconditioning like effect. This cardioprotective effect is called as anesthetic preconditioning (APC). Some clinical data support the cardioprptective effect of valatile anesthetics. The mechanism of APC is thought to be similar to IPC, although the cellular mechanism of APC is not fully investigated. As with IPC, the adenosine triphosphate-regulated potassium (KATP) channel represents the central factor in APC. Our aim is to examine that sevoflurane improves contractile function in stunned myocardium through KATP channel. We planned the experiment following the protocol described by Kersten[10,11]. We showed the effect of cardioprotection by sevoflurane in stunned canine myocardium and the sevoflurane-induced myocardial protection was blocked by glyburide as a KATP channel blocker[4,5,6]. Additionally microscopic myocardial differences were observed after reperfusion in dogs administered no sevoflurane, sevoflurane alone or glyburide prior to sevoflurane.

Methods

Study protocols were approved by the management committee at Jichi Medical Laboratory of Experimental Medicine, based on the school's Guide for Laboratory Animals.

In 22 mongrel dogs weighing 12-27 kg (mean, 18.0 kg), anesthesia was induced using intravenous thiamylal sodium (25 mg/kg). The trachea was intubated without neuromuscular blocking agents and ventilation was adjusted to maintain normocapnia using an R-60 Harvard-type pump respirator (Aika, Tokyo, Japan).

Anesthesia during surgical preparation was maintained by infusion of fentanyl citrate (0.2 $\mu g.kg^{-1}.min^{-1}$), diazepam (0.2 $mg.kg^{-1}.h^{-1}$) and vecuronium bromide (initially 0.2 $mg.kg^{-1}$, more as needed).

Systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP) were measured using a 7F-45326 micromanometer-tipped catheter (Toyoda, Tokyo, Japan) placed through the left femoral artery into the abdominal aorta. A catheter was placed in the abdominal aorta through the right femoral artery for arterial blood sampling. Another catheter was placed in the coronary sinus through the right atrium for coronary venous blood sampling.

Left thoracotomy was performed at the fifth intercostal space. A flow probe was positioned around the ascending thoracic aorta to measure cardiac output (CO). A nylon ligature was placed around the left anterior descending artery (LAD) to allow coronary artery occlusion and reperfusion as needed. A pair of ultrasonic segment length transducers was implanted in the subendocardium of the LAD territory to measure changes in regional contractile function, as percentage segment shortening (%SS). A pressure transducer-tipped catheter was inserted into the left ventricle through an incision in the apex to allow continuous recording of left ventricular (LV) pressure. Maximum rate of increase of LV pressure (LVdp/dt max) was determined by electronic differentiation of LV pressure waveforms. Segment length was

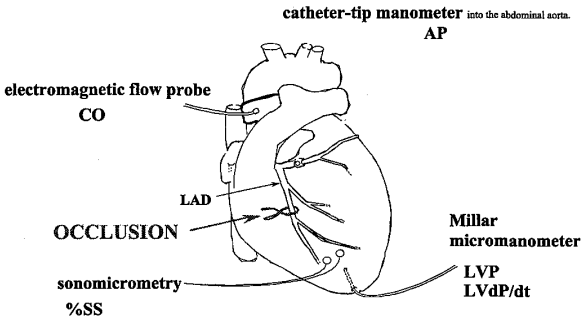


Figure 1 Preparation and monitoring of dog heart.
Cardiac output (CO), left anterior descending artery (LAD), percent segment shortening (% SS), arterial pressure (AP), left ventricular pressure (LVP), rate of increase of LVP (LVdP/dt).

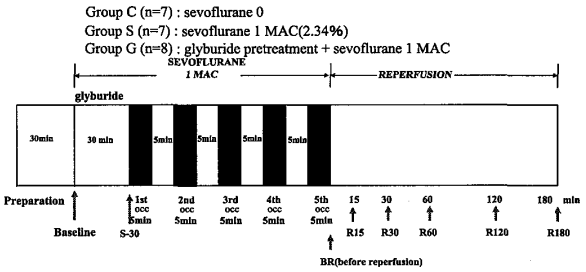


Figure 2 Schematic diagram of experimental protocol. For making stunned myocardium, dogs underwent for 5-minute LAD occlusion interspersed with 5-minute period of reperfusion before 3-hour reperfusion. The mechanism of sevoflurane-induced myocardial protection was investigated in dogs pretreated with glyburide in the presence (Group G) or absence (Group S).

monitored by ultrasonic amplifies. Arterial pressures and surface electrocardiograms were recorded on a multi-channel polygraph (360 ; NEC San-ei, Tokyo, Japan) (Fig. 1).

Stunned myocardium was produced by occluding the LAD 5 times for 5 min each interspersed with 5 min periods of reperfusion before prolonged LAD occlusion. Dogs were instrumented for measurement of heart rate (HR), left ventricular pressunre (LVP) and aortic blood pressure (AP), cardiac output (CO), maximum rate of increase of LV pressure (LVdp/dt max) and percentage segment shortening (%SS). Dogs were randomly divided into 3 groups : Group C, no sevoflurane (n=7) ; Group S, sevoflurane 1MAC anesthesia for 75 min before and after stunning (n=7) ; and Group G, pretreated with glyburide ($0.3 mg \cdot kg^{-1}$) before sevoflurane anesthesia (n=8). Hemodynamic and metabolic variables and LV function were measured in the basal anesthetic state (baseline), after sevoflurane anesthesia for 30 min (S-30), after stunning (before reperfusion ; BR), and at 5 intervals after reperfusion (Fig. 2). After 180 min reperfusion, we injected adequate KCl solution into the central vein of dogs to stop heart beat as soon as possible. Taking hearts out of dogs, we treated them to make histopathological samples. And we observed the microscopic differences in myocardial tissue among groups.

Statistical analysis

All values are expressed as mean ±SEM. Statistical analysis was performed using analysis of variance (ANOVA) with repeated measures, followed by Fischer's protected least significant difference (PLSD). Values of $P<0.05$ were considered statistically significant.

Results

LAD occlusion caused regional dyskinesis in dog hearts. Changes in hemodynamic variables are shown in Table 1. And changes in myocardial metabolic variables are listed in table 2. In Group S compared with Group C, a decrease of MAP was observed from S-30 to R30 ($P<0.01$ till R15, $P<0.05$ at R30). In Group G compared with Group C, a decrease of MAP was observed from S-30 to BR ($P<0,01$). In Group S compared with Group C, a decrease of HR was observed from BR to R15 ($P<0.05$). In Group G compared with Group C, decrease of HR was not observed. In Group S compared with Group C, decrease of CO was observed only at the point of BR ($P<0.05$). In Group G compared with Group C, decrease of CO was not observed. In Group S compared with Group C, decrease of LV dP/dT max was observed from S-30 to R60 ($P<0.01$). In Group G compared with Group C, decrease LV dP/dT max was observed from S-30 to BR, but there were no statistically differences between Group G and Group C after reperfusion.

Regarding %SS, there were no significant differences among groups. But Group S showed faster recovery than Groups C and G in comparison with each baselines. It means that recovery of contractile function was better in Group S than in Groups C and G. In contrast, Group G dogs experienced sustained contractile dysfunction. Changes in metabolic variables are shown in Table 2. We calculated MO2ext.(%) (myocardial oxygen extraction percentage) and MLext.

Table. 1 Changes in hemodynamic variables

	baseline	S-30	BR	R15	R30	R60	R120	R180
MAP (mmHg)								
Group C	104.5±4.8	106.4±5.3	100.7±5.2	110.5±5.7	109.5±4.7	107.8±5.5	107.0±6.2	99.6±5.8
Group S	104.0±8.7	60.9±4.0**‡	60.9±7.4**‡	81.6±6.8**‡	85.1±7.4**†	94.4±7.6	96.0±7.3	95.8±8.1
Group G	105.1±6.9	72.9±5.2**‡	66.3±5.3**‡	97.9±8.5	102.7±7.9	109.4±7.4	109.9±5.7	101.8±5.3
HR (beats · min^{-1})								
Group C	118.5±6.0	119.6±5.9	134.3±7.9	130.0±10.2	122.8±10.0	117.9±10.3	103.4±9.0	100.8±9.3
Group S	107.1±9.1	98.6±5.7	93.3±8.3‡	92.9±9.1†	95.9±8.2	95.1±8.8	97.4±7.4	87.8±6.5
Group G	128.2±6.3	116.5±6.0	109.2±6.1	110.6±7.9	117.0±8.1	112.9±7.1	120.7±8.0	121.6±9.7
CO (littre · min^{-1})								
Group C	3.1±0.5	3.1±0.6	2.9±0.5	2.9±0.5	2.6±0.3	2.5±0.4*	2.4±0.4**	2.4±0.5**
Group S	2.3±0.4	1.9±0.4	1.7±0.3*†	1.8±0.3*	1.9±0.3	2.0±0.3	2.0±0.4	1.9±0.3
Group G	2.5±0.3	2.0±0.3	2.0±0.3	2.2±0.3	2.1±0.4	2.2±0.3	2.4±0.5	2.9±0.6
LV dP/dt max (mmHg · s^{-1})								
Group C	2196±155	2493±228	2376±239	2493±228	2546±248	2506±179	2312±140	2097±121
Group S	2262±202	1170±80‡	1039±109‡	1429±121‡	1588±194‡	1706±152‡	1871±155	1821±132
Group G	2725±162	1849±217†	1398±128‡	2354±215	2604±211	2783±221	2982±223†	2831±193‡
%SS (%)								
Group C	9.47±1.23	9.75±1.62	-5.38±0.75**	4.13±1.84**	6.54±2.08	7.57±2.37	9.70±1.80	6.93±2.05
Group S	10.69±2.00	8.75±1.70	-2.89±1.94**	6.52±2.98	9.03±1.86	8.14±2.72	7.79±2.26	8.96±2.49
Group G	14.63±1.50	12.78±2.45	-4.00±4.40**	8.67±2.16*	8.78±2.15*	9.01±2.57*	10.18±3.10	8.02±3.68*

Values are mean±SEM.

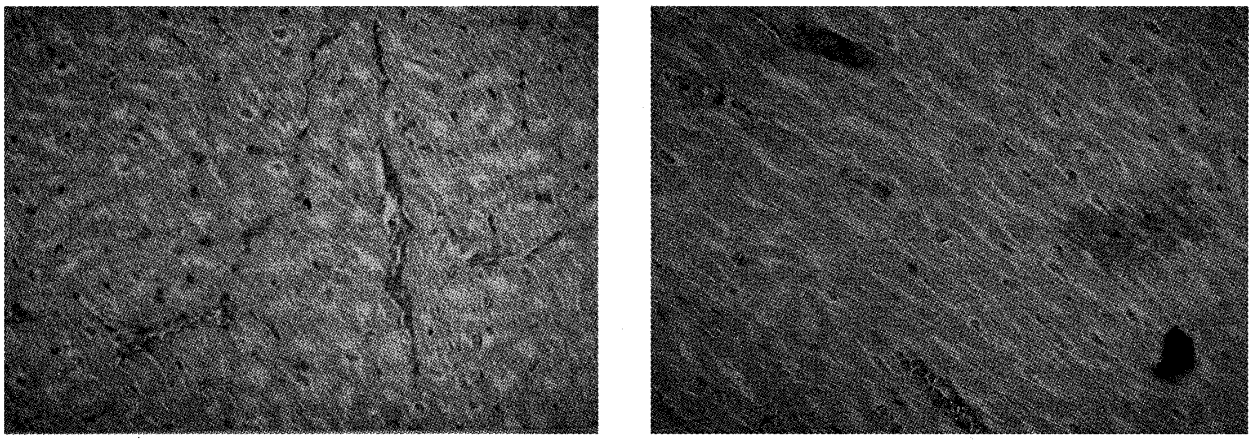
*<0.05, **<0.01 compared with baseline.

†<0.05, ‡<0.01 compared with Group C.

Table. 2 Changes in myocardial metabolic variables

	baseline	S-30	BR	R15	R30	R60	R120	R180
MO2ext. (%)								
Group C	55.7±1.3	55.5±2.0	55.8±2.2	53.0±2.3	54.5±2.2	54.7±3.2	54.7±4.3	51.1±3.8
Group S	52.4±1.7	44.1±4.3	48.4±2.9	48.5±3.2	48.5±4.8	46.4±3.3	44.0±5.1	49.3±3.1
Group G	48.2±3.7	58.2±4.9	59.9±5.3	55.6±5.1	62.9±4.6	52.4±6.2	52.7±5.2	52.0±4.7
MLext. (%)								
Group C	45.3±4.5	48.7±11.1	34.0±5.2	44.0±2.4	37.6±3.4	35.4±4.6	35.0±6.2	37.5±3.6
Group S	46.4±4.2	36.0±4.1	32.2±4.9	44.1±4.2	39.5±5.8	39.9±5.4	40.4±3.8	36.5±7.0
Group G	35.9±5.5	62.1±20.2	37.4±9.7	45.2±9.6	45.6±11.2	41.1±11.1	38.5±9.8	32.2±8.0

Values are mean±SEM.
MO2ext.(%) (myocardial oxygen extraction percentage)
MLext.(%) (myocardial lactate extraction percentage)



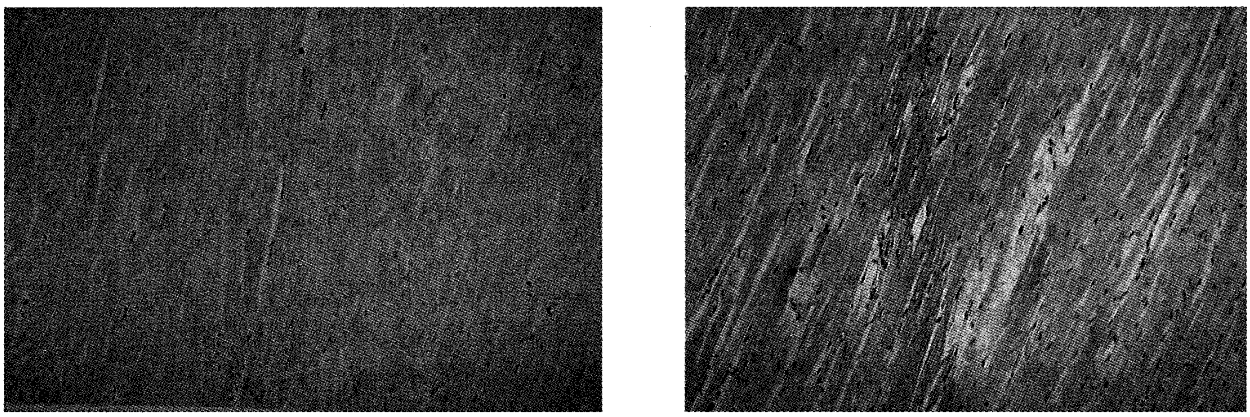
(a) (b)

Figure 3 : Heart muscle in Group C
These are histopathological photomicrographs of a dog heart in Group C. The locations are anterior wall of LV (a), and septum wall of LV(b). There are no findings of myocardial infarction, but both show acidophilic staining changes and infiltration of neutrophils. (Hematoxylin and eosin, x400)

(%) (myocardial lactate extraction percentage) from the data of sampling blood. MO2ext.(%) was measured by the oxygen subtraction between arterial blood gas data and coronary venous blood gas data. And MLext.(%) was calculated by the lactate subtraction of them. There were no significant differences among groups in changes in myocardial metabolic variables. Microscopic images of cardiac muscle samples are shown in Figures 3 and 4. There are no findings of myocardial infarction in all groups.

Discussion

Perioperative cardiac events are closely associated with myocardial ischemia. It has been said that the cardioprotection by anesthetics, especially volatile anesthetics, is effective against myocardial ischemia during operation[1-3]. Ischemic preconditioning (IPC) has been shown to



(a) (b)

Figure 4 : LV anterior wall in Group S and G
The location is anterior wall of LV. (a); In Group S, there are no microscopical abnormalities. (b): In Group G, while there is no tissue necrosis, it shows acidophilic staining changes. (Hematoxylin and eosin, x200)

protect the myocardium against a prolonged ischemic damage. Murry reported the effect of IPC for the first time[7]. IPC reduces myocardial infarct size and severity of myocardial stunning. Myocardial stunning is one of the most important ischmia-reperfusion injuries. Breunwald reported the phenomenon, prolonged post ischemic ventricular dysfunction, as a stunned myocardium[8]. General anesthetics have been reported to protect the myocardium against ischemia-reperfusion injury and to show a rapid recovery of contractile function on myocardial stunning. Warltier reported that volatile anesthetics had a strong preconditioning like effect[9]. This phenomenon is called anesthetic preconditioning (APC), and the cardioprotective effect of volatile anesthetics has been supported by many animal experimental data and some clinical studies.

IPC is clearly effective in protecting the heart from ischemic damage. In addition, APC seems to follow a similar pathway to IPC for protecting the heart. Following the protocol described by Kersten[10,11], stunned myocardium was created in dogs by 5 repeated bouts of ischemia and reperfusion without causing myocardial infarction. Contractile dysfunction represented the major factor in heart dysfunction of the stunned myocardium. We found that sevoflurane enhanced recovery of myocardial contractile function after stunning[4,5]. Sevoflurane administration resulted in earlier recovery of contractile function compared with baseline, and the effects of sevoflurane were blocked by pretreatment with glyburide[6] (Table 1). KATP channel activation by sevoflurane might thus mediate these cardioprotective effects. The preventive effects of sevoflurane against stunning could therefore be considered to mimic the mechanisms of IPC. A series of investigations in experimental animals has found that volatile anesthetics display cardioprotective properties[10-15]. Protection against reversible and irreversible myocardial injury by volatile anesthetics is not easily explained by a simple alteration in myocardial oxygen supply and demand (Table 2). The inability to relate the anti-ischemic effects of volatile anesthetics to improvements in myocardial oxygen supply-demand balance led to the concept that these agents may have direct cardioprotective properties. Volatile anesthetics have been shown to directly precondition or indirectly enhance IPC, resulting in cardioprotec-

tion against myocardial infarction, with KATP channels playing an important role[16,17]. Pharmacological preconditioning produced by volatile agents, including isoflurane, desflurane and sevoflurane, is remarkably similar to IPC and shares many of the same signal transduction elements[18-20]. Kawamura reported that sevoflurane exerts its cardioprotective effects through the prevention of cytokine production[21]. Hara determined the hemodynamic and cardioprotective effects of sevoflurane in canine stunned myocardium[22]. They concluded that sevoflurane exerts a cardioprotective effect that is mediated via activation of KATP channels in ischemic canine hearts. In this report, we studied the hemodynamic and cardioprotective effects of sevoflurane in canine stunned myocardium, separating 22 dogs into 3 groups (Group C, n=7 ; Group S, n=7 ; Group G, n=8). Group G received intravenous glyburide (0.3 mg/kg), a non-selective KATP channel antagonist in the presence of sevoflurane at 1 MAC. Group S received 1 MAC of sevoflurane without pretreating of glyburide. Regional myocardial contractility was evaluated by using %SS. Hara measured %SS before and during 15 min ischemia and 90 min reperfusion[22]. We performed LAD occlusion 5 times for 5 min each interspersed with 5 min periods of reperfusion before reperfusion for 180 min. Hara reported that recovery of %SS by 90 min after reperfusion was significantly improved in dogs anesthetized with sevoflurane, whereas recovery was poor in dogs pretreated with glyburide. We observed the same effect, but the recovery appeared sooner, 15 min after reperfusion. Differences in recovery time between theirs and ours were probably attributable to the effect of IPC. Better cardiac protection might thus be achievable using both APC and IPC. Myocardial metabolic variables showed no significant differences between groups (Table 2). These results indicate that sevoflurane confers cardioprotective effects through the activation of KATP channels and independent from cardiac work. It is said that the decrease of LV dP/dt max is associated with the diminishing of oxygen demand. From the result of this study, we can say that glyburide inhibited diminishing of myocardial oxygen demand.

In addition, this study observed changes in cardiac muscle in each group under hematoxylin and eosin staining (Fig. 3, 4). No myofibrillar degeneration or coagulative myocytolysis was identified, indicating the absence of cardiac infarction in all groups. LV anterior muscle in Group S seemed to be almost normal, but that in Group C and G showed acidophilic staining changes and infiltration of neutrophils into tissue. Heindl showed the myocardial protective effect of sevoflurane by reducing postischemic adhesion of neutrophils in guinea pig heart[23]. In this study, histological differences remained present even after reperfusion for 180 min. In humans, De Hert and colleagues suggested that volatile anesthetics were cardioprotective[1]. They demonstrated that sevoflurane-anesthetized patients displayed reduced cardiac enzyme release and improved left ventricular function after coronary artery bypass graft (CABG), compared to patients anesthetized with propofol. APC combined with IPC (as in this study) may improve cardiac function after CABG.

In conclusion, activation of KATP channels in cardiac muscle produces cardioprotective effects during myocardial ischemia. Sevoflurane enhances the functional recovery of stunned myocardium, and these effects are blocked by the KATP channel antagonist, glyburide. Sevoflurane has a cardioprotective effect that is mediated by activation of KATP channels in

stunned canine myocardium.

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セボフルランはKATPチャンネルを介して犬の気絶心筋の収縮能を改善する

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要　約

本研究の目的は，犬の気絶心筋において，吸入麻酔薬セボフルランによって誘導される心筋保護作用が，KATPチャンネルを介して行われることを調べることにある。気絶心筋は，冠動脈左前下行枝を5回，5分間毎の結紮と解除を繰り返すことによって作成した。22頭の雑種成犬を，コントロール群(n=7)，セボフルラン群(n=7)，グリブライド（KATPチャンネルブロッカー）処理群（n=8）の3群に分けた。血行動態，代謝および酸素需要の変化と心機能を，基礎麻酔下（baseline），30分間のセボフルラン麻酔後（S-30），気絶心筋作成後（再灌流前；BR），再灌流後(15，30，60，120，180min)の8点で測定した。心収縮能の指標である%SS（segment shortening）の回復は，群間比較では有意差は見られなかったが，baselineでの比較ではセボフルラン群で他群より早期(15分後)の回復が見られた。また，グリブライド処理群では，再灌流180分後でも有意に低値であった。心筋組織標本では各群とも梗塞の所見はみられず，セボフルラン群での虚血性変化は他群より軽度であった。

以上より，セボフルランはKATPチャンネルを介して，犬の気絶心筋の収縮能を改善していることが示唆される。

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