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Is Isoflurane-induced Preconditioning Dose Related?

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Background: **Volatile anesthetics precondition against myocardial infarction, but it is unknown whether this beneficial action is threshold- or dose-dependent. The authors tested the hypothesis that isoflurane decreases myocardial infarct size in a dose-dependent fashion *in vivo*.**

Methods: **Barbiturate-anesthetized dogs (n = 40) were instrumented for measurement of systemic hemodynamics including aortic and left ventricular pressures and rate of increase of left ventricular pressure. Dogs were subjected to a 60-min left anterior descending coronary artery occlusion followed by 3 h of reperfusion and were randomly assigned to receive either 0.0, 0.25, 0.5, 1.0, or 1.25 minimum alveolar concentration (MAC) isoflurane in separate groups. Isoflurane was administered for 30 min and discontinued 30 min before left anterior descending coronary artery occlusion.**

Results: **Infarct size (triphenyltetrazolium staining) was 29 ± 2% of the area at risk in control experiments (0.0 MAC). Isoflurane produced significant ($P < 0.05$) reductions of infarct size (17 ± 3, 13 ± 1, 14 ± 2, and 11 ± 1% of the area at risk during 0.25, 0.5, 1.0, and 1.25 MAC, respectively). Infarct size was inversely related to coronary collateral blood flow (radioactive microspheres) in control experiments and during low (0.25 or 0.5 MAC) but not higher concentrations of isoflurane. Isoflurane shifted the linear regression relation between infarct size and collateral perfusion downward (indicating cardioprotection) in a dose-dependent fashion.**

Conclusions: **Concentrations of isoflurane as low as 0.25 MAC are sufficient to precondition myocardium against infarction. High concentrations of isoflurane may have greater efficacy to protect myocardium during conditions of low coronary collateral blood flow.**

VOLATILE anesthetics protect myocardium against stunning and infarction. These beneficial actions appear to occur through a signal transduction pathway that is remarkably similar to that observed during ischemic preconditioning (IPC). Activation of adenosine receptors,[1–3] protein kinase C,[2,4] inhibitory guanine regulatory proteins,[5] and mitochondrial and sarcolemmal adenosine triphosphate–regulated potassium (K_{ATP}) channels[6–9] have been implicated in anesthetic-induced preconditioning. Isoflurane-induced preconditioning and IPC decrease myocardial infarct size by 50–60%.[2,7,9–11] Controversy exists as to whether IPC or K_{ATP} channel agonists reduce infarct size through threshold- or dose-dependent mechanisms. Whether a threshold concentration of isoflurane less than 1 minimum alveolar concentration (MAC) protects myocardium from infarction is also unknown. We tested the hypothesis that isoflurane decreases myocardial infarct size in a dose-dependent manner using a range of concentrations between 0.25 and 1.25 MAC. We also evaluated the relation between myocardial infarct size and coronary collateral blood flow in the presence and absence of isoflurane to determine if this relation is altered by the anesthetic agent.

Methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care and Use Committee of the Medical College of Wisconsin. All conformed to the *Guiding Principles in the Care and Use of Animals* of the American Physiologic Society and were in accordance with the *Guide for the Care and Use of Laboratory Animals*.[12]

General Preparation

Surgical implantation of instruments has been previously described in detail.[6] Briefly, dogs were anesthetized with sodium barbital (200 mg/kg) and sodium pentobarbital (15 mg/kg) and ventilated using positive pressure with an air and oxygen mixture after tracheal intubation. End-tidal concentrations of isoflurane were measured at the tip of the endotracheal tube by an infrared anesthetic analyzer. A 7-French, dual micromanometer-tipped catheter was inserted into the aorta and left ventricle (LV) for measurement of aortic and LV pressures and the maximum rate of increase of LV pressure ($+dP/dt_{max}$). Heparin-filled catheters were inserted into the left atrial appendage and the right femoral artery for administration of radioactive microspheres and withdrawal of reference blood flow samples, respectively. A 1-cm segment of the left anterior descending coronary artery (LAD) immediately distal to the first diagonal branch was isolated, and a silk ligature was placed around the vessel for production of coronary artery occlusion and reperfusion. Hemodynamics were continuously monitored on a polygraph and digitized using a computer interfaced with an analog-to-digital converter.

Experimental Protocol

Baseline hemodynamics were recorded 90 min after instrumentation was completed. All dogs were subjected

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to a 60-min LAD occlusion followed by 3 h of reperfusion. Dogs were randomly assigned to receive 0.0, 0.25, 0.5, 1.0, and 1.25 MAC isoflurane in separate experimental groups. The canine MAC of isoflurane used in the current investigation was 1.28%.[13] Isoflurane was administered for 30 min and discontinued 30 min before LAD occlusion. Regional myocardial blood flow was measured 30 min before and during LAD occlusion, and 60 min after the onset of reperfusion. Dogs that developed intractable ventricular fibrillation and those with subendocardial collateral blood flow greater than 0.15 ml · min^{-1} · g^{-1} were excluded from data analysis.[14]

Measurement of Myocardial Infarct Size

At the end of each experiment, myocardial infarct size was measured as previously described.[15] The LV area at risk (AAR) for infarction was separated from the normal area (stained with Patent blue dye), and the two regions were incubated at 37°C for 20–30 min in 1% 2,3,5-triphenyltetrazolium chloride in 0.1 M phosphate buffer adjusted to pH 7.4. After overnight storage in 10% formaldehyde, infarcted and noninfarcted myocardium within the AAR were carefully separated and weighed. Infarct size was expressed as a percentage of the AAR.

Determination of Regional Myocardial Blood Flow

Carbonized plastic microspheres (15 ± 2 μm [SD] in diameter) labeled with ^{141}Ce, ^{103}Ru, or ^{95}Nb were used to measure regional myocardial perfusion as previously described.[6] Transmural tissue samples were selected from the ischemic region (distal to the LAD occlusion) and were subdivided into subepicardial, midmyocardial, and subendocardial layers of approximately equal thickness. Samples were weighed, placed in scintillation vials, and the activity of each isotope was determined. Similarly, the activity of each isotope in the reference blood flow sample was assessed. Tissue blood flow (milliliters per minute per gram) was calculated as $Q_r \cdot C_m \cdot C_r^{-1}$, where Q_r indicates the rate of withdrawal of the reference blood flow sample (milliliters per minute), C_m indicates the activity (counts per minute per gram) of the myocardial tissue sample, and C_r indicates the activity (counts per minute) of the reference blood flow sample. Transmural blood flow was considered as the average of subepicardial, midmyocardial, and subendocardial blood flows. Coronary collateral blood flow was measured in the central ischemic zone (LAD perfusion area) after 30 min of coronary artery occlusion.

Statistical Analysis

Statistical analysis of data within and between groups was performed with analysis of variance for repeated measures followed by Student-Newman-Keuls test. The relation between myocardial infarct size and coronary collateral blood flow was evaluated with linear regression analysis. Analysis of covariance was used to compare regression relations among groups. Changes within and between groups were considered statistically significant when the P value was < 0.05. All data are expressed as mean ± standard error of the mean.

Results

Forty dogs were instrumented to obtain 36 successful experiments. Four dogs were excluded from the overall analysis because subendocardial collateral blood flow was greater than 0.15 ml · min^{-1} · g^{-1} (1, 0.0 MAC; 2, 0.25 MAC; and 1, 0.5 MAC). These four dogs were included in the specific analysis of the relation between coronary collateral blood flow and myocardial infarct size.

Systemic Hemodynamics

There were no differences in hemodynamics between experimental groups during baseline conditions (table 1). Isoflurane caused dose-dependent decreases in heart rate, mean arterial and LV systolic pressures, and LV $+dP/dt_{max}$. Heart rate and mean arterial pressure returned to baseline values within 30 min after discontinuation of isoflurane in dogs receiving concentrations less than 1.0 MAC. In contrast, mean arterial and LV systolic pressures remained depressed during LAD occlusion and reperfusion in dogs receiving 1.25 MAC isoflurane as compared with control experiments. There were no differences in hemodynamics between groups after 3-h reperfusion.

Myocardial Infarct Size and Coronary Collateral Blood Flow

The LV AAR was similar between groups (control, 37 ± 2; 0.25 MAC isoflurane, 40 ± 2; 0.5 MAC isoflurane, 40 ± 3; 1.0 MAC isoflurane, 38 ± 1; 1.25 MAC isoflurane, 44 ± 2% of LV mass). Myocardial infarct size expressed as a percentage of the AAR was 29 ± 2% (n = 8) in dogs that did not receive isoflurane (0.0 MAC). Isoflurane (0.25, 0.5, 1.0, and 1.25 MAC) reduced infarct size to 17 ± 3 (n = 8), 13 ± 1 (n = 7), 14 ± 2 (n = 7), and 11 ± 1% (n = 6) of the AAR, respectively (fig. 1). An inverse relation between myocardial infarct size and coronary collateral blood flow was observed in dogs receiving 0.0, 0.25, and 0.5 MAC isoflurane (fig. 2). Isoflurane also caused a dose-related downward shift in the regression relation. Infarct size was unrelated to coronary collateral blood flow during 1.0 and 1.25 MAC isoflurane (fig. 3). There were no differences in transmural myocardial perfusion during control conditions and after 1-h reperfusion among groups (table 2). Coronary collateral blood flow was also similar among all groups.

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Table 1. Systemic Hemodynamics

				Reperfusion (h)		
	Baseline	Intervention	30 min CAO	1	2	3
HR (beats/min)						
CON	129 ± 6	129 ± 7†	125 ± 6	127 ± 10	125 ± 9	126 ± 9
$ISO_{0.25\ MAC}$	127 ± 8	124 ± 8†	127 ± 6	117 ± 5	120 ± 5	124 ± 4
$ISO_{0.5\ MAC}$	124 ± 3	110 ± 5	114 ± 4	107 ± 6	111 ± 7	111 ± 8
$ISO_{1.0\ MAC}$	137 ± 3	111 ± 1*	126 ± 2	123 ± 4	126 ± 6	132 ± 8
$ISO_{1.25\ MAC}$	129 ± 4	95 ± 6*‡	112 ± 3*	105 ± 5*	103 ± 5*	106 ± 5*
MAP (mmHg)						
CON	106 ± 8	108 ± 8	100 ± 9	107 ± 9	110 ± 8	108 ± 9
$ISO_{0.25\ MAC}$	90 ± 4	81 ± 5†‡	87 ± 3	94 ± 2	94 ± 5	97 ± 4
$ISO_{0.5\ MAC}$	102 ± 4	79 ± 4*†‡	92 ± 4	100 ± 3	102 ± 4	105 ± 4
$ISO_{1.0\ MAC}$	106 ± 3	65 ± 3*‡	92 ± 3*	94 ± 4*	99 ± 3	100 ± 5
$ISO_{1.25\ MAC}$	104 ± 7	56 ± 5*‡	80 ± 5*	83 ± 3*‡	85 ± 5*‡	90 ± 5*
LVSP (mmHg)						
CON	116 ± 7	115 ± 7	112 ± 10	117 ± 11	118 ± 8	115 ± 10
$ISO_{0.25\ MAC}$	104 ± 3	92 ± 6†‡	95 ± 3	101 ± 3	99 ± 5	102 ± 3
$ISO_{0.5\ MAC}$	113 ± 5	84 ± 5*†‡	97 ± 4*	104 ± 4	107 ± 4	110 ± 4
$ISO_{1.0\ MAC}$	115 ± 4	72 ± 3*‡	97 ± 2*	98 ± 4*	103 ± 4*	102 ± 4*
$ISO_{1.25\ MAC}$	115 ± 6	60 ± 4*‡	84 ± 6*‡	85 ± 3*‡	88 ± 6*‡	95 ± 5*
LVEDP (mmHg)						
CON	6 ± 1	4 ± 1	15 ± 3*	15 ± 3*	15 ± 3*	14 ± 3*
$ISO_{0.25\ MAC}$	6 ± 1	5 ± 1	9 ± 2†	11 ± 2*	9 ± 2	9 ± 2
$ISO_{0.5\ MAC}$	8 ± 2	9 ± 1‡	14 ± 2	19 ± 3*	15 ± 2*	17 ± 2*
$ISO_{1.0\ MAC}$	7 ± 1	9 ± 1‡	15 ± 2*	15 ± 2*	15 ± 3*	14 ± 2*
$ISO_{1.25\ MAC}$	6 ± 2	8 ± 2‡	19 ± 3*‡	19 ± 2*	18 ± 3*	13 ± 2*
+dP/dtmax (mmHg/s)						
CON	1,920 ± 160	1,870 ± 150	1,610 ± 180	1,630 ± 210	1,580 ± 150	1,490 ± 200*
$ISO_{0.25\ MAC}$	1,870 ± 90	1,720 ± 190†	1,630 ± 110	1,510 ± 120	1,420 ± 130	1,490 ± 110
$ISO_{0.5\ MAC}$	1,750 ± 120	1,180 ± 60*‡	1,540 ± 130	1,400 ± 50*	1,430 ± 40*	1,370 ± 70*
$ISO_{1.0\ MAC}$	2,020 ± 140	1,030 ± 50*‡	1,590 ± 100*	1,470 ± 100*	1,480 ± 80*	1,470 ± 100*
$ISO_{1.25\ MAC}$	1,760 ± 110	830 ± 50*‡	1,300 ± 120*	1,380 ± 70*	1,290 ± 140*	1,230 ± 70*

Data are mean ± standard error of the mean.

* Significantly ($P < 0.05$) different from baseline. † Significantly ($P < 0.05$) different from the respective value during 1.25 minimum alveolar concentration (MAC) isoflurane. ‡ Significantly ($P < 0.05$) different from the respective value during control (0.0 MAC) experiments.

CAO = coronary artery occlusion; HR = heart rate; MAP = mean aortic pressure; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; $+dP/dt_{max}$ = maximal rate of increase of left ventricular pressure; CON = control; ISO = isoflurane.

Discussion

A minimum duration of ischemia is required to activate endogenous protective signal transduction during IPC. For example, an ischemic duration between 2 and 3 min alone[16–19] is insufficient to produce IPC. This threshold may be pharmacologically altered. Administration of K_{ATP} channel agonists[18,20] or an allosteric enhancer of the A_1 adenosine receptor[17] in doses that are insufficient to elicit protection alone decrease the time threshold of IPC. Volatile anesthetics also activate K_{ATP} channels and A_1 receptors, but whether a minimal threshold dose of these agents is required to produce myocardial protection is unknown. The current study was designed to examine if isoflurane-induced preconditioning is dose-related.

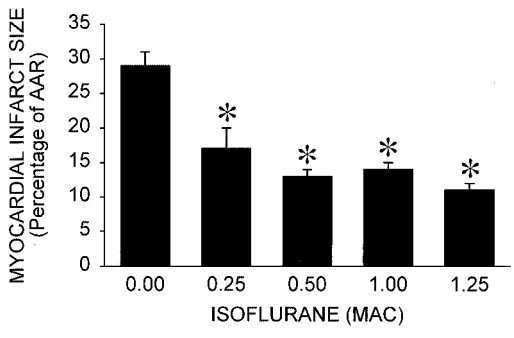

Fig. 1. Myocardial infarct size expressed as a percentage of the area at risk (AAR) in dogs receiving isoflurane (0.25, 0.5, 1.0, or 1.25 minimum alveolar concentration [MAC]). *Significantly ($P < 0.05$) different from control experiments (0.0 MAC).

Our results indicate that concentrations of isoflurane as low as 0.25 MAC are sufficient to precondition myocardium against infarction. These data contrast with our previous findings demonstrating that 1 MAC sevoflurane does not protect against infarction when this anesthetic is washed out 30 min before coronary artery occlusion.[16] Sevoflurane appears to retain a significantly shorter "memory" than that characteristic of isoflurane[7] and IPC,[19] which allows myocardium to remain resistant to infarction after the initial preconditioning stimulus is removed. Nevertheless, previous exposure to sevoflu-

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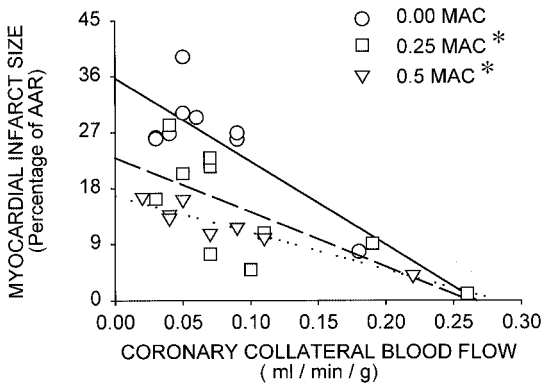

Fig. 2. Relation between myocardial infarct size and coronary collateral blood flow in dogs receiving isoflurane (0.0, 0.25, or 0.5 minimum alveolar concentration [MAC]). An inverse relation was observed in each group (0.0 MAC: y = −1.33.8x + 35.7, r = −0.78, *P* = 0.01; 0.25 MAC: y = −87.6x + 22.9, r = −0.72, *P* = 0.02; 0.5 MAC: y = −59.1x + 16.8, r = −0.94, *P* = 0.001). The infarct size-collateral flow relation was shifted downward by 0.25 or 0.5 MAC isoflurane. *Significantly (*P* < 0.05) different from control experiments (0.0 MAC).

rane reduced the time threshold for IPC to occur.[16] Taken together, these results suggest that the threshold concentration required to precondition myocardium may be specific for a given volatile anesthetic agent and, furthermore, may differ depending on the length of exposure or the duration of the washout or memory period.

Whether further myocardial protection may be conferred by additional ischemic episodes or higher doses of pharmacologic agonists after an initial threshold stimulus is exceeded is highly controversial. A single 5-min coronary artery occlusion reduced infarct size to a similar extent as multiple (2–12) episodes of preconditioning ischemia in dogs[21,22] and rabbits.[19] In contrast, results of another study indicated that a single episode of IPC decreased myocardial infarct size by only 40%, but three sequential episodes markedly reduced infarct size by nearly 100%.[23] Preconditioning with adenosine is dose-dependent,[24] but the K_{ATP} channel agonist bimakalim produced equivalent reductions in infarct size in one study when administered at concentrations that varied by 30-fold.[25] More recently, diazoxide was shown to produce dose-dependent protection against infarction in dogs that may be attributable to activation of both mitochondrial and sarcolemmal K_{ATP} channels.[26]

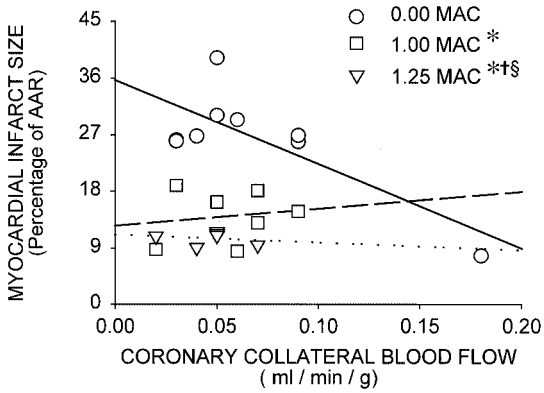

Fig. 3. Relation between myocardial infarct size and coronary collateral blood flow in dogs receiving isoflurane (0.0, 1.0, or 1.25 minimum alveolar concentration [MAC]). Myocardial infarct size is decreased by 1.0 or 1.25 MAC isoflurane independent of coronary collateral blood flow (1.0 MAC: y = 26.5x + 12.6, r = 0.16, *P* = nonsignificant; 1.25 MAC: y = −12.5x + 11.2, r = −0.21, *P* = nonsignificant). The regression relation is shifted downward by isoflurane in a dose-related fashion. *Significantly (*P* < 0.05) different from control experiments (0.0 MAC). †Significantly (*P* < 0.05) different from experiments during 0.25 MAC. §Significantly (*P* < 0.05) different from experiments during 0.5 MAC.

The current results suggest that isoflurane-induced reduction in myocardial infarct size may be dose-dependent, but this effect is only evident in the presence of low coronary collateral blood flow. Infarct size was approximately 10% of the AAR in dogs receiving 1.25 MAC isoflurane, with coronary collateral blood flows that ranged between 0.02 and 0.07 ml · min^{-1} · g^{-1}. In contrast, lower concentrations (0.25 or 0.5 MAC) of isoflurane did not appear to reduce infarct size to this degree (approximately 18%) in experiments in which coronary collateral blood flow was less than 0.05 ml · min^{-1} · g^{-1}. The importance of collateral blood flow as a determinant of infarct size during low but not high concentrations of isoflurane is similar to findings observed during IPC. The extent of infarction has been demonstrated to be inversely related to collateral blood flow in pigs subjected to a 3-min episode of preconditioning ischemia, and the regression relation is shifted downward when compared with control experiments.[27] A 10-min preconditioning episode shifted the regression relation further downward to such a degree that infarct size was no longer dependent on collateral blood flow. Thus, the current and previous results suggest that evaluation of the relation between infarct size and collateral blood flow may be a sensitive method of determining whether anesthetic-induced preconditioning is dose-related.

Isoflurane produced dose-related decreases in heart rate, arterial pressure, and LV dP/dt_{max}. Isoflurane was discontinued 30 min before the LAD occlusion, but the hemodynamic effects of the 1.25 MAC concentration persisted into the reperfusion period. Alterations in myocardial metabolism during and after the administration of isoflurane may be partially responsible for the protection against infarction observed in dogs receiving higher concentrations of this agent. We and other investigators have previously demonstrated that the protective effects of volatile anesthetics were abolished by K_{ATP} channel antagonists. This action was observed despite the presence of similar hemodynamic conditions with or without K_{ATP} channel blockade.[7,8,16] Thus, it appears unlikely that hemodynamic effects of higher concentra-

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Table 2. Transmural Perfusion in the Ischemic (LAD) Region (ml · min^{-1} · g^{-1})

	Baseline	30 min CAO	1 h Reperfusion
CON	0.75 ± 0.10	0.06 ± 0.01*	2.01 ± 0.18*
$ISO_{0.25\ MAC}$	1.03 ± 0.13	0.07 ± 0.01*	2.06 ± 0.31*
$ISO_{0.5\ MAC}$	0.70 ± 0.07	0.06 ± 0.01*	1.68 ± 0.15*
$ISO_{1.0\ MAC}$	0.63 ± 0.08	0.06 ± 0.01*	1.75 ± 0.35*
$ISO_{1.25\ MAC}$	0.81 ± 0.13	0.05 ± 0.01*	1.29 ± 0.14*

Data are mean ± standard error of the mean.

* Significantly ($P < 0.05$) different from baseline.

LAD = left anterior descending coronary artery; CAO = coronary artery occlusion; CON = control; ISO = isoflurane.

tions of isoflurane are solely responsible for reductions in infarct size observed in the current or previous investigations. However, the results of experiments conducted in barbiturate-anesthetized dogs may or may not be similar to those observed in conscious dogs or humans.

The area of the LV at risk for development of infarction and degree of coronary collateral blood flow are important determinants of the extent of myocardial infarction. However, no differences in these variables accounting for the current findings were observed among experimental groups. The relation between collateral blood flow and infarct size was also directly evaluated and compared between groups. The contribution of specific signal transduction elements to the protection afforded by different concentrations of isoflurane was not evaluated in the current investigation. Evidence suggests that multiple episodes of IPC may activate both protein kinase C– and tyrosine kinase–mediated pathways, in contrast to a single preconditioning stimulus.[21,28] Whether higher concentrations of or prolonged exposure to isoflurane recruits additional pathways that may also be responsible for myocardial protection will require additional investigation. It is also possible that low concentrations of isoflurane activate only one K_{ATP} channel subtype, whereas high concentrations activate both sarcolemmal and mitochondrial K_{ATP} channels. Both channels have been shown to be important during ischemic[26] and anesthetic-induced preconditioning[8] in dogs. This hypothesis will require further evaluation *in vitro*.

In conclusion, the results demonstrate that low concentrations of isoflurane are sufficient to precondition against infarction, but the efficacy of 0.25 or 0.5 MAC isoflurane to decrease infarct size may be diminished in the presence of low coronary collateral blood flow. High concentrations of isoflurane (1.0 or 1.25 MAC) produce profound and equivalent protective effects independent of the extent of coronary collateral perfusion.

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