Effects of Alcohol Consumption on Cardiovascular Events in Male Patients With Healed Myocardial Infarction

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Background In Western countries, many studies have shown that among healthy people moderate drinkers have a lower incidence of cardiovascular events than abstainers and heavy drinkers. However, it is not clear whether this is true in patients with a healed myocardial infarction (MI).

Methods and Results In the present study cardiovascular events were defined as cardiac events or strokes. Male patients only were included because the incidence of cardiovascular events is low in females. In patients younger than 65 years, the incidence of cardiovascular events was 34.6 persons per year (54 cases: 3.9%) of abstainers, 17.4 persons per year (20 cases: 1.9%) of moderate drinkers ($p < 0.01$ vs abstainers) and 30.3 persons per year (18 cases: 3.2%) of heavy drinkers. However, in those aged 65 years or older, the incidence was 47.8 persons per year (24 cases: 4.5%) of abstainers, 58.4 persons per year (14 cases: 5.6%) of moderate drinkers, and 314.8 persons per year (12 cases: 19.7%) of heavy drinkers. In this age group, cardiovascular events were significantly higher in heavy drinkers than in the other 2 groups ($p < 0.01$), and the incidence was not lower in the moderate drinkers than in abstainers as shown in the younger group.

Conclusions In patients younger than 65 years with a healed MI, drinking limited less than 30 ml/day (moderate intake) reduces the incidence of cardiovascular events, but not in those aged 65 years or older. (Circ J 2006; 70: 1263–1268)

Key Words: Alcohol consumption; Cardiovascular events; Myocardial infarction

It has been shown that cardiovascular events,¹ as well as mortality,² are reduced with moderate alcohol consumption and increased with heavy drinking, showing a J-shaped curve. Reduced risk in moderate drinkers is attributed to the reduction in coronary heart disease³ and cardiovascular events.⁴ The biological mechanism of reducing cardiovascular events induced by moderate alcohol consumption is related to the beneficial effects on high-density lipoprotein (HDL),⁵ hemostatic factors⁶ and an anti-inflammatory mechanism.⁷ However, the influence of drinking by patients with a healed myocardial infarction (MI) has not been clarified^{8–10} nor has it been investigated whether this relationship is modified by age. Because the degree of “moderate” alcohol consumption will differ between Japanese and Western populations, we need to know the relationship in Japanese patients. It has been reported that hypertension, diabetes, smoking, hyperlipidemia, obesity, and family history are important coronary risk factors for men,^{11–14} but the risk of alcohol consumption for those with a healed MI has not been determined and that was the aim of the present study.

Methods

Patient Enrolment, Study Period and Exclusion Criteria

All male patients with an acute MI or previous MI treated

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at the Department of Cardiology, Kinki University Hospital were retrospectively registered from January 1986 to December 1999, totaling 5,323 excluding ex-drinkers who had been abstainers during the study period (703), those whose onset of MI was unknown (256) and those lost to follow-up (15). Drinking habit was established using either a questionnaire or from the hospital record. The diagnosis of acute MI was made according to the characteristic clinical symptoms, ECG findings, and increased cardiac enzymes at onset. Follow-up was ceased when the patient died or moved to another hospital. Patients whose alcohol consumption was unknown (1,478) were excluded from the study. Consequently, 3,845 males were subjected to analysis.

Cardiovascular Events

Fatal and non-fatal recurrent MI, death from heart failure, and sudden death were defined as cardiac events. Fatal and nonfatal cerebral infarction, fatal and nonfatal cerebral bleeding were defined as a stroke. Transient ischemic attacks and cardiogenic cerebral embolism were not included as stroke. Either a cardiac event or stroke was defined as a cardiovascular event. The diagnostic criteria for recurrent MI were the same as used for MI at registration. The diagnosis of death from heart failure was made when the death was directly caused by heart failure; sudden death was diagnosed according to the definition of Braunwald.¹⁵ The diagnosis of stroke was made according to medical history, physical examination, and findings of computed tomography and magnetic resonance imaging.

Classification of Alcohol Consumption

We distributed the alcohol consumption questionnaire to inpatients and outpatients, or investigated the alcohol con-

Table 1 Baseline Characteristics of Male Patients Aged Less Than 65 Years and 65 Years or Older With a Healed Myocardial Infarction Recruited During 1986–1999, Kinki University Hospital, Japan

	Age <65 years			Age ≥65 years		
	Abstainers (n=1,377)	Moderate drinkers <30 ml/day (n=1,064)	Heavy drinkers ≥30 ml/day (n=562)	Abstainers (n=533)	Moderate drinkers <30 ml/day (n=248)	Heavy drinkers ≥30 ml/day (n=61)
Age at onset of MI (years)	54.6±7.2	52.8±7.1**	51.2±8.9**	71.3±5.3	70.8±4.4	70.6±3.7
Blood pressure						
Systolic (mmHg)	124±18	121±17**	123±18	126±21	128±19	126±23
Diastolic (mmHg)	74±12	73±11*	74±11	72±13	72±11	73±12
Heart rate (beats/min)	65±11	65±11	64±10	67±12	65±11	69±11
Time interval from onset to registry (months)	36.3±43.8	41.4±49.9**	32.6±41.1	32.3±40.5	24.7±37.3*	8.8±22.4**
Mean observation time (months)	13.6±17.6	13±16.8	12.7±16.1	11.3±13.9	11.6±14.2	7.5±11
Infarct site						
Anterior (%)	45.1	42.3	36.1**	38.8	24.2**	24.6*
Inferior (%)	27.2	32.4**	26.7	26.1	38.7**	36.1
Non-Q-wave (%)	19.3	14.7**	27.2**	19.7	20.2	8.2*
Multiple or others (%)	8.4	10.6	10.0	15.4	16.9	31.1**
Forrester class (I/II III IV)	590/229	415/118*	238/91	134/97	109/63	19/13
Killip class (I/II III IV)	718/107	460/88	288/41	205/31	153/23	21/11**
No. of coronary vessels involved	1.7±0.8	1.7±0.8	1.5±0.8**	1.7±0.9	1.8±0.8	2.4±1.3**
Wall motion index by echocardiogram	7.6±5.5	6.5±5.2**	6.1±4.7**	8.8±5.9	6.5±5.7**	9.1±7.2
Post-MI angina (%)	29.4	23.1**	24.8	26.2	29.0	50.9**
Vasospastic angina (%)	3.8	3.8	12.8**	2.1	10.9**	4.9
Positive exercise ECG test (%)	39.5	39.2	31.1**	44.3	53.8	74.1**
Interventional therapy						
Coronary thrombosis (%)	47.4	40.5*	49.6	35.3	45.9*	40.4
PCI (%)	35.0	36.6	29.3	17.1	28.5**	14.0
CABG (%)	11.5	12.2	5.5	14.8	5.9**	5.3
Coronary risk factors						
Hyperlipidemia (%)	51.8	57.9**	57.5*	27.5	36.0*	47.4**
Hypertension (%)	38.7	40.2	52.8**	45.5	49.6	25.0**
Smoking (%)	83.3	79.9*	89.0**	63.2	82.2**	60.4
Diabetes mellitus (%)	28.0	33.7**	28.6	27.6	20.6*	23.6
Obesity (%)	31.7	24.0**	30.6	17.5	17.7	21.4
Gout (%)	11.7	14.7	20.8**	6.0	13.0**	0.0
Laboratory findings						
Total cholesterol (mg/dl)	199±38	201±36	204±37*	193±34	187±35	187±38
Triglycerides (mg/dl)	161±88	163±97	167±94	136±66	147±80	118±47
HDL-cholesterol (mg/dl)	39±11	43±12**	46±15**	41±11	41±12	46±10*
Medications						
Antiplatelet agents (%)	73.2	75.4	72.1	72.6	76.6	62.3
-blockers (%)	65.9	66.6	63.4	51.8	51.6	32.8**
Cholesterol-lowering agents (%)	44.7	51.5**	46.8	25.1	29.4	13.1*
ACE inhibitors (%)	24.5	23.3	24.4	22.9	26.6	13.1
Warfarin (%)	32.5	33.1	25.1**	16.0	25.4**	26.2
Calcium antagonists (%)	50.5	47.5	53.6	49.5	57.3*	70.5**
Nitrates (%)	57.4	60.2	61.0	63.0	64.9	62.3
Antiarrhythmic agents (%)	8.1	5.9	7.4	10.2	16.5*	18.9

* $p<0.05$, ** $p<0.01$ (Abstainers vs Moderate drinkers, Heavy drinkers).

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; HDL, high-density lipoprotein; ACE, angiotensin-converting enzyme.

sumption using the hospital records. Ethanol content differs among beverages: 5% for beer, 15% for Japanese sake, 45% for whiskey, and 25% for shochu (a clear distilled liquor). Because the average amount of ethanol ingested by the study patients was 29.7 ml/day, we classified less than 30 ml/day as moderate drinking and at least 30 ml/day as heavy drinking. We defined abstainers as those who had never drunk alcohol and ex-drinkers as those who were drinking in the past but had stopped drinking during the study period.

Classification of Age

The age of the patients was defined by the age at onset of MI: younger group (<65 years) and older group (≥65 years).

Follow-up (Table 1)

Pulse rate and blood pressure were measured in the ward during the daily check-up of inpatients. ECG, echocardiography and blood tests were performed at least once a week. Outpatients were followed up at regular monthly visits to the clinic and for them ECG, echocardiography and blood tests were performed twice a year on average. The clinical severity of MI was evaluated by Killip¹⁶ and Forrester¹⁷ classifications. Wall motion indexes¹⁸ on echocardiography and QRS scores¹⁹ on ECG were used as indicators of infarct size. The diagnoses of effort and variant angina pectoris were made according to characteristic clinical symptoms, ECG and coronary angiographic findings.

Statistical Analysis

All data are expressed as the mean±standard deviation

Table 2 Cardiovascular Events Among 3 Groups of Patients With a Healed Myocardial Infarction Recruited During 1986–1999, Kinki University Hospital, Japan

	Patients younger than 65 years			Patients 65 years or older		
	Abstainers (n=1,377) 1,000 person per year	Moderate drinkers (n=1,064) 1,000 person per year	Heavy drinkers (n=562) 1,000 person per year	Abstainers (n=533) 1,000 person per year	Moderate drinkers (n=248) 1,000 person per year	Heavy drinkers (n=61) 1,000 person per year
Cardiovascular events OR (95% CI)	34.6 1	17.4* 0.49 (0.28–0.89)	30.3 0.87 (0.53–1.43)	47.8 1	58.4 1.24 (0.83–1.83)	314.8** 9.15 (6.65–12.60)
		1.77 (0.97–3.20)			7.41 (5.51–9.96) ^{††}	
Fatal recurrent MI	6.4	1.7	6.7	2	0	26.2** ^{††}
Non-fatal recurrent MI	20.5	10.4	16.8	15.9	25	183.6** ^{††}
Sudden death	3.2	4.3	5	10	12.5	78.7** ^{††}
Death from worsening heart failure	1.3	0	1.7	6	8.3	26.2** ^{††}
Cerebral infarction	1.9	0.9	0	13.9	12.5	0** ^{††}
Cerebral bleeding	1.3	0	0	0	0	0
Cardiac death	10.9	6.1	13.5	17.9	20.9	131.1** ^{††}
Non-cardiac death	9	6.1	3.4	23.9	20.9	52.5** ^{††}
Total mortality OR (95% CI)	19.9 1	12.1 0.60 (0.29–1.24)	16.8 0.84 (0.44–1.62)	41.8 1	41.7 1.00 (0.64–1.55)	183.6** ^{††} 5.16 (3.64–7.31)

OR, odds ratio; CI, confidence interval. Other abbreviation see in Table 1.

* $p < 0.05$, ** $p < 0.01$ (Abstainers vs Moderate drinkers, Heavy drinkers), ^{††} $p < 0.01$ (Moderate vs Heavy drinkers).

(SD). Comparisons of the mean values of cardiovascular events among the 3 groups were made using the χ^2 test. The difference in the incidence of cardiovascular events among the 3 groups was tested using odds ratio (OR) and 95% confidence intervals (CI). To assess the possible effects of patient characteristics, subgroup analyses were carried out within the strata of 74 variables. Multivariate analysis of independent predictors of events was performed using the Cox hazard model with a forward stepwise method. The significance of the incidence of events over time was evaluated using the log-rank test after obtaining event-free ratios using the Kaplan-Meier estimation method. The probability values were 2-sided, and values of $p < 0.05$ were considered significant. We also calculated the OR and 95% CI for all possible risks.

Results

Cardiovascular events in this group of male patients were 37.7 persons per year (78 cases, 4.1%) in abstainers, 24.5 persons per year (34 cases, 2.6%) in moderate drinkers, and 47.4 persons per year (30 cases, 4.8%) in heavy drinkers, showing significantly less incidence in moderate drinkers than in the heavy drinkers ($p < 0.01$). The 3,845 patients were divided into 2 groups according to age (Table 2): 3,003 patients younger than 65 years (1,377 abstainers, 1,064 moderate drinkers, 562 heavy drinkers), and 842 patients aged 65 years or older (533 abstainers, 248 moderate drinkers, 61 heavy drinkers). The age at onset of MI was 57.2 ± 10.2 years, the time interval from onset to registry was 35.5 ± 44.5 months and the mean observation time was 12.8 ± 16.4 months in the male patients. As shown in Table 1, there were considerable differences in the basic characteristics of the patients in the 3 groups. HDL-cholesterol (C) showed a tendency to increase with increased amounts of alcohol. The heavy drinkers in the group aged 65 years or older had more multivessel disease, positive ECG test and more were taking calcium antagonists, and less were taking β -blockers.

In addition, there were some differences in the observation period, so we calculated by 1,000 persons per year.

Cardiovascular Events and Total Mortality (Table 2)

We investigated whether the beneficial effects of moderate alcohol consumption might be modified by age. In patients younger than 65 years, cardiovascular events occurred significantly less in moderate drinkers than in abstainers ($p < 0.01$; OR 0.49; 95% CI 0.28–0.89). However, in those aged 65 years or older, the incidence of cardiovascular events in moderate drinkers was not reduced compared with the abstainers and it was significantly increased in heavy drinkers compared with abstainers and moderate drinkers. This increase was statistically significant for fatal and non-fatal recurrent MI, sudden death and death from worsening heart failure.

Cardiovascular events occurred in 25.5 persons per year (22 cases) in ex-drinkers. In those younger than 65 years, cardiovascular events occurred in 21.7 persons per year (14 cases), which was not a significant difference compared with the other 3 groups. But in those aged 65 years or older, cardiovascular events occurred in 36.6 persons per year (8 cases), which was a significant decreased compared with moderate drinkers and heavy drinkers.

Subgroup Analysis

Because this study was retrospective, there were significant differences in the patient characteristics, so subgroup analyses were made for 37 items (74 subgroups). In all of the subgroups, there were less cardiovascular events in moderate drinkers compared with abstainers younger than 65 years old. This tendency was not observed in the subgroups of patients aged 65 years or older. However, there were much cardiovascular events in heavy drinkers compared with abstainers in these older patients.

Multivariate Analysis (Table 3)

Multivariate analysis was carried out using the Cox

Table 3 Multivariate Analysis Among 3 Groups of Patients With a Healed Myocardial Infarction Recruited During 1986–1999, Kinki University Hospital, Japan

	Hazard ratio	95%CI Lower–Upper
<i>Patients younger than 65 years (Cox-Hazard Model)</i>		
CABG	0.05	0.01–0.49*
Atrial fibrillation	0.24	0.03–1.85
PCI	0.52	0.27–0.99*
Moderate drinker	0.56	0.32–0.97*
Cholesterol-lowering agents	0.57	0.34–0.94*
Obesity	0.63	0.35–1.13
Antiplatelet agents	0.67	0.42–1.06
-blockers	0.80	0.50–1.26
Warfarin	0.87	0.52–1.46
Forrester class	0.87	0.57–1.35
Nitrates	0.90	0.57–1.43
Heavy drinker	0.92	0.51–1.66
Coronary thrombolysis	0.92	0.55–1.54
Calcium antagonists	0.92	0.57–1.47
Diabetes mellitus	0.94	0.57–1.56
Smoking	1.02	0.53–1.96
PVC	1.02	1.00–1.04*
Gout	1.15	0.63–2.11
Killip class	1.31	0.83–2.06
ACE inhibitors	1.39	0.85–2.28
Vasospastic angina	1.41	0.62–3.21
Hyperlipidemia	1.54	0.93–2.54
Multivessel disease	1.55	1.14–2.10**
Hypertension	1.59	0.98–2.59
Positive exercise ECG	1.63	0.97–2.72
Antiarrhythmic agents	2.05	1.07–3.93*
Angina pectoris	3.18	1.96–5.15**
<i>Patients 65 years or older (Cox-Hazard Model)</i>		
Obesity	0.10	0.02–0.62*
CABG	0.21	0.23–1.91
Positive exercise ECG	0.49	0.17–1.39
Antiplatelet agents	0.59	0.30–1.16
Warfarin	0.62	0.24–1.62
-blockers	0.64	0.33–1.26
Calcium antagonists	0.65	0.34–1.28
Gout	0.75	0.16–3.58
Smoking	0.84	0.40–1.76
Hyperlipidemia	0.88	0.38–2.06
Vasospastic angina	0.91	0.18–4.74
Killip class	0.93	0.46–1.89
PVC	0.97	0.94–1.00
Forrester class	0.97	0.57–1.65
Moderate drinker	1.02	0.44–2.35
ACE inhibitors	1.06	0.43–2.62
Hypertension	1.11	0.53–2.34
Age	1.12	1.05–1.19**
Nitrates	1.26	0.63–2.52
Cholesterol-lowering agents	1.33	0.59–2.97
PCI	1.33	0.45–3.93
Coronary thrombolysis	1.41	0.62–3.20
Atrial fibrillation	1.60	0.52–4.91
Diabetes mellitus	1.96	0.89–4.29
Multivessel disease	2.45	1.41–4.26**
Antiarrhythmic agents	2.85	1.25–6.49*
Angina pectoris	3.34	1.61–6.95**
Heavy drinker	5.75	2.21–14.90**

PVC, premature ventricular contraction. Other abbreviations see in Tables 1, 2.
* $p < 0.05$, ** $p < 0.01$.

hazard model among all items of the patients' backgrounds. In the group younger than 65 years, moderate drinking was an independent predictor for reduced incidence of cardiovascular events ($p < 0.05$; hazard ratio 0.56; 95% CI 0.32–0.97). On the other hand, in those aged 65 years or older,

Fig 1. Event-free curves for cardiovascular events in patients aged less than 65 years and 65 years or older with healed myocardial infarction recruited during 1986–1999, Kinki University Hospital, Japan.

heavy drinking was an independent predictor of increased cardiovascular events ($p < 0.01$; hazard ratio 5.75; 95% CI 2.21–14.90).

Kaplan-Meier Curve

The event-free curves for cardiovascular events by the Kaplan-Meier method indicated that the incidence of cardiovascular events was lower in the moderate drinkers than in abstainers younger than 65 years, whereas in heavy drinkers aged 65 years or older, it was significantly higher than in the other 2 groups (Fig 1).

Discussion

The results of the present study show that male patients who consume less than 30 ml/day of ethanol had a lower incidence of cardiovascular events than abstainers, provided they are younger than 65 years of age. This favorable effect did not extend to those aged 65 years or older, and alcohol consumption in these aged patients increased the incidence of cardiovascular events.

Relationship Between Alcohol Consumption and Cardiovascular Events

We found that the relationship between alcohol consumption and cardiovascular events was J-shaped in male patients aged less than 65 years but not in the elderly. In those aged 65 years or older, cardiovascular events were increased, even more in moderate drinkers than in abstainers, but especially increased in heavy drinkers. These increases were the result of increases in non-fatal recurrent MI and sudden death. It is noteworthy that the beneficial effects of moderate drinking for reducing cardiovascular events seen in patients younger than 65 years were not apparent in the older patients.

We excluded 1,078 female patients with a healed MI because cardiovascular events occurred in 45.8 (38 cases/888 cases) persons per year in abstainers, 32.1 (5 cases/156 cases) persons per year in moderate drinkers, and 0 (0 cases/34 cases) persons per year in heavy drinkers. Consequently there was a low number of total cardiovascular events, especially in heavy drinkers, and we considered it was not possible to analyse the data from the female patients.

Our results coincide with those in a report by Muntwyler et al¹⁸ who showed total mortality and cardiovascular death in patients with MI were increased by alcohol consumption. In patients aged 65 years or older, cardiac death was significantly increased in heavy drinkers, more than in the other 2 groups. It is well proven that overindulgence, with too much drinking or stress, on holidays will contribute to death from arrhythmias (holiday heart).²⁰ A population study conducted by Klöner et al also demonstrated that excessive drinking or overindulgence will increase the incidence of coronary death.²¹ Taivainen et al²² emphasized an acute water imbalance as an important causative factor for the increased cardiovascular events following alcohol drinking. Drinking alcohol increases urinary output, serum osmolality and also serum sodium concentration for 4h, resulting in significant water loss and dehydration. After 4h, the vasopressin concentration is elevated and serum osmolality and serum Na concentration are reduced. Thus, after drinking, there will be a temporal change in blood pressure as well as heart rate.

In the present study, in those aged 65 years or older, the incidence of cardiovascular events in moderate drinkers was not reduced compared with the abstainers and it was significantly increased in heavy drinkers compared with abstainers and moderate drinkers. Older patients, who have less tolerance of transient water imbalance or neurohormonal changes, will be more susceptible to coronary events.

Possible Mechanism to Reduce the Cardiovascular Events by Moderate Alcohol Consumption in Patients Younger Than 65 Years

It has been shown that alcohol consumption increases HDL-C and apolipoprotein levels;⁵ hemostatic factors that prolongs bleeding time and plasma concentration of fibrinogen, von Willebrand factor and VII factor;⁶ decreases the plasma concentration of C-reactive protein and interleukin-6 through an anti-inflammatory mechanism.⁷ These changes may play a role in reducing the incidence of cardiovascular events in moderate drinkers. Although we did not measure the hemostatic factor or the anti-inflammatory factor in this study, we consider that they are intricately involved in the reduction of cardiovascular events. Although HDL-C will increase with increasing amounts of alcohol, subgroup

analysis failed to show a reduction in the incidence of cardiovascular events with an increase in HDL-C. The beneficial effects of moderate alcohol consumption may not be elicited solely by changes in blood components but may be also due to a relaxation of attitude, which cancels out the stress. Sympathetic nerve excitement accompanying stress is known to be an independent factor in the occurrence of cardiovascular events. The effects of moderate alcohol consumption in reducing stress and sympathetic nerve excitement may play a beneficial preventive role.

Influence of Heavy Alcohol Consumption

Heavy alcohol consumption increased the incidence of cardiovascular events and total mortality in any age group in this study. Population studies also show that increased alcohol consumption increases hypertension, stroke, cardiomyopathy, arrhythmias, cancer, suicide, and traffic accidents in general, but that these will be increased in heavy drinkers. Chicago epidemiological studies²³ indicated that heavy drinking increases the incidence of sudden death. In the present study also, heavy drinking was associated with an increase of sudden death in older people, which was in agreement with other reports.²⁴

Mukamal et al⁶ reported that higher intake of alcohol is associated with impaired fibrinolytic potentials. Thevananther and Brechen²⁵ have reported the direct action of acetaldehyde as a cause of the increase in the incidence of cardiovascular events associated with heavy drinking. Drinking has a diuretic action, promotes urination, and causes water imbalance, which eventually leads to dehydration that in turn will influence the renin-angiotensin-aldosterone system, increasing serum renin activity, angiotensin II and aldosterone. Because neuronal imbalance is not well tolerated in older people, such an imbalance may cause cardiovascular events in older patients particularly.

Alcohol Consumption and Stroke

The relationship between alcohol consumption and cerebral infarction also showed a J-curve relationship;²⁶ and moderate alcohol consumption significantly reduced the risk of cerebral infarction. The preventive mechanism⁸ of moderate drinking for stroke is similar to that for coronary artery disease. The significant increase in the incidence of cerebral hemorrhage with increasing alcohol consumption is related to alcohol-induced hypertension.²⁷ In the present study, we could not clarify this relationship because the incidence of both cerebral infarction and bleeding was very small at 0.4% and 0.05%, respectively.

Study Limitations

This is the first cohort study done in Japan to elucidate the relationship between alcohol consumption and cardiovascular events in post-MI patients. However, it has several limitations, the greatest of which is the non-randomized protocol, although ethical considerations prevent us from conducting a randomized study. However, the subgroup analyses as well as multivariate analyses were conducted to overcome these shortcomings.

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