

Autonomic Neuropathy and the Ventilatory Responses of Diabetics to Progressive Hypoxemia and Hypercarbia

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SUMMARY

To investigate one suggested cause of unexplained deaths of diabetic patients with autonomic neuropathy, ventilatory responses to progressive hypoxemia and to progressive hypercarbia were compared among two groups of diabetic patients, with and without autonomic neuropathy, and a group of normal control subjects. Hypoxemia was induced gradually under isocapnic conditions and the arterial oxygen saturation was reduced to below 75%. In a separate test the end tidal CO₂ was increased gradually to 55 mm Hg in subjects who could tolerate this degree of hypercarbia. The ventilatory responses to hypoxemia and to hypercarbia did not differ among groups nor did age, duration of diabetes, or presence of proliferative retinopathy and nephropathy have a significant effect on the ventilatory responses of diabetics. The authors conclude that defective ventilatory responses to hypoxemia or hypercarbia are not associated with the sudden unexplained deaths in diabetics with autonomic neuropathy. *DIABETES* 31:609-614, July 1982.

Diabetic patients with symptomatic autonomic neuropathy (AN) have a poor prognosis.¹ Renal and cardiovascular disease account for the majority of deaths among these patients, but a significant number of deaths remain unexplained.² Page and Watkins observed a series of patients with AN who suffered unexpected cardiorespiratory arrests.³ These episodes were not due to obvious cardiac causes and may have been the result of defective respiratory reflexes. Since the cardiorespiratory arrests all occurred in circumstances that could have led to hypoxia, the researchers speculated that diabetic patients may have abnormal responses to hypoxemia. They also advised that drugs with central respiratory de-

pressant effects should be used with caution in diabetics with AN. Ewing et al.,⁴ reporting in a preliminary communication, were unable to confirm that diabetics with AN have abnormal responses to hypoxemia. However, recent sleep studies of diabetics have supported the hypothesis that AN may be associated with abnormal ventilation: three of eight patients with AN had over 30 episodes of apnea lasting more than 10 s during the course of one night's sleep, in contrast to diabetics without AN who never experienced more than 10 episodes of apnea during the same period of time.⁵

The parasympathetic system plays an important part in ventilation because the carotid and aortic bodies are innervated by the glossopharyngeal and vagus nerves. Destruction or denervation of both carotid bodies in the dog results in virtually complete loss of the ventilatory response to hypoxia.⁶ On the other hand, the role of the aortic bodies in the response to hypoxemia is small and unimportant compared with that of the carotid bodies.⁷ Vagal afferent information is required to produce an increased rate of breathing in response to hypoxemia or hypercarbia⁸ and the vagus nerve modulates the depth and frequency of breathing both during wakefulness and during sleep.⁹ However, cervical blockade of the vagus does not affect the ventilatory response to exercise or to hyperthermia⁸ nor does it alter the basic respiratory pattern for each stage of sleep.⁹ These reflexes, which occur independent of afferent vagal impulses, are mediated by higher cerebral centers, possibly in the hypothalamus.

Sensitive cardiac tests of autonomic neuropathy have indicated that parasympathetic function may be impaired at diagnosis or within a few years of the diagnosis of diabetes and before obvious symptoms of AN occur.¹⁰ However, episodes of unexplained cardiorespiratory arrest only seem to affect diabetics who have severe disease and advanced AN.¹¹ The present study investigated the integrity of the ventilatory responses of diabetics with symptomatic AN. Their responses to hypoxemia and to hypercarbia were compared with those of diabetics without AN and with those of normal control subjects.

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PATIENTS AND METHODS

Subject selection. Twenty-one insulin-dependent diabetics, all known diabetics for at least 10 yr, were included in this study. They are subdivided into two groups on the basis of autonomic neuropathy. Ten patients had classic features of AN: 5 had postural hypotension; 5 loss of warning symptoms of hypoglycemia; 3 diabetic gastroparesis and/or diabetic diarrhea; and 2 an atonic bladder. The diagnosis of AN was confirmed when, using an EKG, the following three acknowledged cardiac tests of AN were found abnormal for all 10 patients: (1) a variation in heart rate of less than 9 bpm between inspiration and expiration during deep breathing at six breaths per minute;¹² (2) a result of <1.2 for the ratio between the longest R-R interval after the Valsalva maneuver and the shortest R-R interval during the maneuver;¹³ (3) a result of 1.0 or less for the ratio between the R-R intervals of the 30th and 15th heart beats on assuming standing from the lying position.¹⁴ The remaining 11 diabetic patients in this study had no symptoms of AN and had normal heart rate responses.

The clinical features of the two groups of diabetics are shown in Table 1. Seven females and three males had AN; seven females and four males were free of AN. The age (mean \pm 1 SD) of patients with AN was 34 ± 14.7 yr, not significantly different from the age (35.8 ± 12.8 yr) of patients without AN. Patients with and without AN had a duration of disease of 17.9 ± 8.8 and 22 ± 10.2 yr, respectively ($P > 0.05$). Although retinopathy affected all patients, proliferative retinopathy was more common (6 of 10 patients) in the group with AN than in the group without AN (3 of 11 pa-

tients). Nephropathy, defined according to the criteria of Deckert and Poulsen,¹⁵ affected 6 of 10 patients with AN and 2 of 11 patients without AN. The serum creatinine was less than 2.0 mg/dl in all patients studied except two. These patients (nos. 15 and 16) had AN and their serum creatinine levels were 4.1 and 5.7 mg/dl, respectively. Peripheral neuropathy was diagnosed in patients with sensory or motor symptoms and abnormal deep tendon reflexes or impaired sensation. All the diabetics with AN and three patients without AN had peripheral neuropathy. Symptomatic postural hypotension (systolic drop in blood pressure of 20 mm Hg or more) was recorded in five patients with AN but not in patients without AN. None of the diabetic patients studied had a history of previous cardiopulmonary disease. Only the two diabetics with a serum creatinine greater than 2.0 mg/dl were anemic: their hemoglobin levels were 10.0 and 10.5 g/dl, respectively. At the time of the study the diabetic patients had a glycosylated hemoglobin (HbA_{1c}) level that varied between 9% and 12.5% (normal 5.0–8.5%).

Seventeen healthy normal subjects (8 males and 9 females) who had no history of diabetes mellitus or cardiopulmonary disease served as controls for this study. Their age was 30.0 ± 9.2 yr, not significantly different from the age of the two groups of diabetics.

Informed consent was obtained from all subjects participating in the study and the project was approved by the Human Subjects Committee.

Methods. Pulmonary function tests including forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), maximum voluntary ventilation (MVV), and single breath carbon

TABLE 1
Clinical features of diabetic patients with and without autonomic neuropathy

Patient no.	Sex	Age (yr)	Duration of diabetes (yr)	Retinopathy*	Nephropathy	Peripheral neuropathy	Blood pressure (mm Hg)		Heart rate ¹² variation during deep breathing (beats/min)	Valsalva ¹³ heart rate ratio	Lying-to ¹⁴ -standing heart rate ratio
							Supine	Standing			
Diabetics without autonomic neuropathy											
1	F	22	16	+	0	0	130/70	128/78	14	1.24	1.33
2	F	23	10	+	0	0	124/62	130/70	13	1.35	1.29
3	F	26	14	++	0	0	132/84	130/88	17	1.29	1.35
4	F	26	16	+	+	0	142/88	140/90	15	1.40	1.22
5	M	29	25	++	0	+	130/70	138/74	10	1.31	1.22
6	F	32	27	+	0	0	120/80	140/80	20	1.35	1.23
7	M	38	25	+	0	0	100/65	110/70	15	1.21	1.32
8	M	44	14	+	0	0	130/75	140/80	13	1.60	1.16
9	F	44	16	+	0	0	120/60	116/80	18	1.47	1.20
10	M	46	37	++	+	+	138/70	132/72	15	1.33	1.12
11	F	64	42	+	0	0	132/62	130/60	14	1.39	1.10
Diabetics with symptomatic autonomic neuropathy											
12	M	20	16	++	+	+	130/90	125/90	7	1.07	1.00
13	F	24	10	++	+	+	150/110	110/80	0	1.00	1.00
14	F	26	18	++	+	+	130/95	130/95	4	1.06	0.93
15	F	26	20	++	+	+	140/90	90/60	4	1.00	1.00
16	M	27	20	++	+	+	140/96	120/80	0	1.00	1.00
17	F	28	15	+	0	+	125/75	120/70	6	1.14	1.08
18	F	28	20	+	+	+	130/75	150/85	7	1.00	0.94
19	F	50	10	+	0	+	148/90	110/80	4	1.11	1.00
20	F	58	10	+	0	+	160/88	110/70	5	1.00	0.94
21	M	58	40	++	0	+	140/70	125/65	0	1.16	1.00

* Retinopathy: ++ indicates proliferative retinopathy and + indicates background retinopathy.

monoxide diffusion were performed on a CPI 5000 Pulmolab using computer program Set No. 1 for normative data. Results of FVC, FEV₁, MVV, and single breath carbon monoxide diffusion were expressed as percent of the predicted values.

Ventilatory responses to progressive hypoxemia and to progressive hypercarbia were tested separately using standard rebreathing techniques that yield reproducible results in individual subjects.^{16,17} With a nose clip in place the patient breathed into a closed-circuit system (Collins Modular Lung Analyzer). The system contained a 9-L recording spirometer for holding premixed gas and for measurement of minute ventilation (expired volume per minute or V_e). During induction of hypoxemia a carbon dioxide absorber with a variable bypass allowed the operator to regulate inspired CO₂ and thereby to maintain a constant end tidal CO₂ (P_{ET}CO₂) between 38 and 42 mm Hg. In this test the arterial blood oxygen saturation (O₂ Sat) was gradually lowered below 75%. During the hypercarbic challenge O₂ was supplemented to maintain a fractional inspired oxygen of 0.40. The end tidal CO₂ (P_{ET}CO₂) was gradually increased to 55 mm Hg or more but the test was terminated earlier if the patient showed signs of distress. O₂ Sat was monitored with a Hewlett Packard Model 47201A ear lobe oximeter. P_{ET}CO₂ was monitored at the mouthpiece with a Beckman LB-2 Medical Gas Analyzer.

The ventilatory responses (V_e) to progressive hypoxemia were recorded at 1-min intervals and at 5% changes in oxygen saturation, and the ventilatory responses to hypercarbia were also recorded at 1-min intervals and at 5-mm Hg changes in P_{ET}CO₂. The responses of individual patients to the two separate challenges were fitted to a straight line by the method of least squares, thereby generating slopes and intercepts. For purposes of further analysis of the ventilatory responses to hypoxemia the average of the V_e determinations (L/min) obtained at four different levels of O₂ Sat (>95%, 94–85%, 84–75%, <75%) has been used. Similarly, the average of the V_e determinations obtained at four different levels of P_{ET}CO₂ (<45, 46–50, 51–55, >55 mm Hg) has been used for further analysis of the ventilatory responses to hypercarbia.

RESULTS

Diabetics with AN had an FVC (mean ± 1 SD) of 89.3 ± 15.0% (of predicted values) and an FEV₁ of 94.3 ± 16.5%. Diabetic patients without AN had a similar FVC (91.3 ± 9.3%) and FEV₁ (93.7 ± 8.2%). MVV was

82.9 ± 17.9% in patients with AN and 96.5 ± 16.6% in diabetic patients without AN (P > 0.05). Single breath carbon monoxide diffusion was only studied in six patients with AN and four patients without AN, and the results were 108 ± 26% and 104 ± 29%, respectively (P > 0.05).

Table 2 shows the slopes (b₁) and intercepts (b₀) for the ventilatory responses to hypoxemia and hypercarbia among diabetic patients with and without AN and normal control subjects. Using a one-way analysis of variance no significant differences were identified among the three groups.

The ventilatory responses to hypoxemia and to hypercarbia of individual diabetic patients with and without AN are shown in Table 3. The mean responses for the group of normal control subjects are also shown. As demonstrated in Table 3, while all patients and controls completed the hypoxemic challenge test, several subjects (seven diabetics without AN, six diabetics with AN, and nine controls) were unable to complete the hypercarbic challenge test. In order to retain all the available data, the ventilatory responses to hypoxemia of the two sets of diabetics and of controls were compared at four different levels of O₂ saturation using a nonparametric analysis of variance;¹⁸ no significant differences were found among the three groups. Similarly, the ventilatory responses to hypercarbia of the three groups were compared at four different levels of P_{ET}CO₂ and no significant differences were identified among groups. Using a repeated measures analysis of variance with one trial factor and one grouping factor¹⁹ and restricting the analysis to diabetic patients and controls who had complete studies to hypoxemia and to hypercarbia, there was still no significant group effect for either the ventilatory response to hypoxemia or the ventilatory response to hypercarbia.

Among the diabetic patients with AN 5 of 10 had symptomatic postural hypotension. The ventilatory responses of these five patients (nos. 13, 15, 16, 19, 20) were therefore compared with the responses of the remaining patients in this group who did not have postural hypotension. Statistical analysis, using an independent groups t test, failed to reveal any difference in the response to hypoxemia. However, during the hypercarbic challenge diabetics with postural hypotension had a significantly higher (t₀) = 2.75, P = 0.025) ventilatory response at P_{ET}CO₂ < 45 mm Hg but not at P_{ET}CO₂ levels above 45 mm Hg. The slopes and intercepts for the ventilatory responses to progressive hypoxemia and to progressive hypercarbia were similar for patients with and without postural hypotension.

In Table 4 the diabetic subjects are subdivided into

TABLE 2
The intercepts (b₀) and slopes (b₁) for the ventilatory responses of diabetics and control subjects

	Ventilatory responses to hypoxemia*		Ventilatory responses to hypercarbia†	
	b ₀ ± 1 SD (L/min)	b ₁ ± 1 SD (L/min/% O ₂ Sat)	b ₀ ± 1 SD (L/min)	b ₁ ± 1 SD (L/min/mm P _{ET} CO ₂)
Diabetics without AN	10.20 ± 5.18	0.97 ± 0.71	-56.96 ± 44.86	1.59 ± 0.98
Diabetics with AN	8.40 ± 8.04	1.21 ± 0.49	-70.29 ± 33.74	1.72 ± 0.69
Control subjects	12.34 ± 8.00	1.41 ± 0.73	-91.80 ± 28.32	2.21 ± 0.57

* The slope (b₁) for the ventilatory response to hypoxemia represents the change in ventilation per unit change in oxygen saturation and the intercept (b₀) indicates the extrapolated value for ventilation at 100% O₂ Sat.

† The slope (b₁) for the ventilatory response to hypercarbia represents the change in ventilation per unit change in P_{ET}CO₂, over the range where this relationship is linear. The intercept (b₀) indicates the extrapolated value for ventilation when P_{ET}CO₂ is 0.

TABLE 3
Ventilatory responses to the hypoxemic and hypercarbic challenges

Patient No.	Ventilatory response (L/min) to hypoxemia				Ventilatory response (L/min) to hypercarbia			
	Arterial oxygen saturation (%)				End tidal CO ₂ (mm Hg)			
	>95	94–85	84–75	<75	<45	46–50	51–55	>55
Diabetics without autonomic neuropathy								
1	10.8	25.5	37.2	51.3	8.2	—	—	—
2	27.7	54.8	70.2	76.9	18.0	—	—	—
3	18.5	40.7	—	63.4	15.8	31.3	—	—
4	11.4	16.3	27.0	39.4	8.4	15.4	26.1	41.8
5	11.6	14.8	16.2	27.0	10.9	13.8	15.5	17.8
6	7.7	12.4	17.8	25.9	6.0	9.9	14.9	—
7	12.2	17.0	—	21.6	7.5	10.8	16.1	22.9
8	9.6	13.6	18.2	21.6	9.1	13.7	20.0	—
9	9.9	11.5	21.0	37.5	8.2	12.8	16.3	16.7
10	10.4	23.5	38.6	52.3	8.5	15.6	27.8	—
11	8.9	10.3	11.9	15.1	7.8	13.6	—	—
Mean ± 1 SD	12.6 ± 5.7	21.8 ± 14.0	28.7 ± 18.1	39.3 ± 19.6	9.8 ± 3.7	15.2 ± 6.3	19.5 ± 5.3	24.8 ± 11.7
Diabetics with symptomatic autonomic neuropathy								
12	7.6	11.3	19.6	51.1	6.2	14.0	26.7	—
13	23.3	32.4	—	59.4	14.5	30.6	—	—
14	18.0	32.4	—	59.4	5.9	7.1	12.8	—
15	16.3	27.9	29.0	29.7	10.2	19.7	24.8	—
16	10.0	15.4	33.8	58.1	9.2	14.3	21.6	—
17	8.4	15.2	17.6	20.3	7.2	11.5	14.8	20.4
18	9.8	23.1	42.5	51.3	9.4	14.5	18.4	21.6
19	12.5	19.6	27.0	33.8	17.3	35.1	—	—
20	6.5	11.6	28.4	37.8	9.5	11.6	23.3	36.5
21	14.5	19.6	29.0	44.5	8.2	11.7	19.2	33.8
Mean ± 1 SD	12.7 ± 5.3	20.8 ± 7.9	28.4 ± 7.7	44.5 ± 13.7	9.8 ± 3.6	17.0 ± 9.0	20.2 ± 4.8	28.0 ± 8.3
Controls								
Mean ± 1 SD	17.0 ± 7.6 (N = 17)*	26.8 ± 13.5 (N = 17)	39.3 ± 19.6 (N = 15)	51.3 ± 23.4 (N = 14)	9.1 ± 1.9 (N = 17)	14.1 ± 4.0 (N = 15)	23.5 ± 5.4 (N = 14)	31.2 ± 7.7 (N = 8)

* Figures in parentheses indicate number of controls studied.

groups to investigate the effect of age, duration of diabetes, and the presence of proliferative retinopathy and nephropathy on ventilatory responses. Both a nonparametric analysis of variance and a repeated measures analysis of variance showed that age, duration of diabetes, severity of diabetic retinopathy, and presence of nephropathy did not have a significant effect on the ventilatory responses to hypoxemia or hypercarbia. Moreover, there was no significant difference between the ventilatory responses of normal control subjects and any of the diabetic subgroups.

DISCUSSION

Earlier studies²⁰ and the observations of Page and Watkins³ and others^{21,22} had suggested that autonomic neuropathy may lead to abnormal ventilatory responses to hypoxemia. In addition, studies both in dogs and in man have shown the important role of the vagus in controlling ventilatory responses through receptors in the carotid bodies.^{6–8} However, in some of these studies findings attributed to vagal denervation may have been influenced to some extent by damage or destruction of sympathetic fibers to the carotid bodies.²³ The patients with AN included in the present study had symptoms and, although we did not specifically test

their sympathetic responses, it is also likely that at least five of these subjects with postural hypotension had disease of the sympathetic as well as the parasympathetic system. Yet we did not find any differences between the ventilatory responses of diabetics with or without AN and normal control subjects. Even among diabetics with postural hypotension there was no evidence of impairment of ventilatory responses. Watkins and MacKay have emphasized that only patients with severe complicated disease and advanced AN are at risk of unexpected respiratory arrests.¹¹ All the diabetics we studied had long-standing disease (> 10 yr duration) and retinopathy but the severity of the diabetes, as assessed by the stage of their retinopathy and the presence of nephropathy, did not influence the ventilatory responses to hypoxemia or hypercarbia. Our definition of diabetic nephropathy was based on proteinuria (> 500 mg/24 h) and only two patients had a serum creatinine above 2.0 mg/dl. Therefore, it remains possible that the ventilatory responses of diabetics with more severe nephropathy may be abnormal. We have previously described a diabetic patient with severe AN who sustained repeated episodes of prolonged apnea and hypoxemia during hemodialysis.²⁴ Others have observed hypoapnea and hypoxemia among both diabetic

TABLE 4
The ventilatory responses of diabetic patients according to age, duration of diabetes, retinopathy, and nephropathy

	Ventilatory response (L/min) to hypoxemia				Ventilatory response (L/min) to hypercarbia			
	Arterial oxygen saturation (%)				End tidal CO ₂ (mm Hg)			
	>95	94-85	84-75	<75	<45	46-50	51-55	>55
Age ≤35 yr	13.9 ± 6.3 (13)*	24.7 ± 12.8 (13)	31.0 ± 16.4 (10)	47.1 ± 17.2 (10)	9.9 ± 3.8 (13)	16.5 ± 7.8 (11)	19.5 ± 5.3 (9)	25.4 ± 11.0 (4)
Age >35 yr	10.5 ± 2.5 (8)	15.8 ± 4.7 (8)	24.9 ± 8.6 (7)	33.0 ± 12.6 (8)	9.5 ± 3.2 (8)	15.6 ± 8.0 (8)	20.4 ± 4.5 (6)	27.4 ± 9.3 (4)
Duration of diabetes ≤20 yr	13.3 ± 6.1 (15)	23.4 ± 12.5 (15)	30.9 ± 14.5 (12)	46.0 ± 16.2 (15)	10.5 ± 3.9 (15)	17.8 ± 8.7 (13)	20.4 ± 4.8 (10)	27.4 ± 11.0 (5)
Duration of diabetes >20 yr	10.9 ± 2.4 (6)	16.2 ± 4.8 (6)	22.7 ± 10.9 (5)	31.0 ± 14.2 (6)	8.1 ± 1.6 (6)	12.5 ± 2.1 (6)	18.7 ± 5.3 (5)	24.8 ± 8.1 (3)
Background retinopathy	12.2 ± 6.5 (12)	20.5 ± 12.7 (12)	29.2 ± 17.2 (10)	37.7 ± 18.7 (12)	10.2 ± 4.0 (12)	16.4 ± 8.8 (10)	17.6 ± 3.1 (7)	23.6 ± 7.5 (5)
Proliferative retinopathy	13.1 ± 3.8 (9)	22.4 ± 9.6 (9)	27.6 ± 7.7 (7)	47.2 ± 13.0 (9)	9.2 ± 2.9 (9)	15.8 ± 6.6 (9)	21.8 ± 5.5 (8)	31.1 ± 12.2 (3)
Nephropathy absent	12.2 ± 5.6 (13)	20.5 ± 13.1 (13)	26.7 ± 16.1 (11)	36.6 ± 18.2 (13)	10.3 ± 4.0 (13)	16.0 ± 8.6 (11)	17.5 ± 3.0 (8)	24.6 ± 8.4 (8)
Nephropathy present	13.3 ± 5.3 (8)	22.7 ± 7.9 (8)	31.7 ± 8.2 (6)	50.0 ± 10.5 (8)	9.0 ± 2.6 (8)	16.4 ± 6.7 (8)	22.6 ± 5.4 (7)	31.7 ± 14.3 (2)

* Figures in parenthesis indicate number of patients studied.

and nondiabetic patients on hemodialysis.²⁵ In all these cases the dialysis solution contained acetate, which probably led to decreased ventilation secondary to loss of carbon dioxide in the dialysis bath and a reduction of carbon dioxide output at the lungs. However, it still remains unclear whether in these circumstances diabetics are more likely to develop severe hypoxemia than nondiabetics.

Our findings demonstrate that impaired ventilatory responses to hypoxemia and hypercarbia do not explain the high incidence of unexpected deaths among diabetic patients with symptomatic AN.² Therefore, other possible explanations for these deaths need to be considered. Although the vagus nerve is involved in the ventilatory responses to hypoxemia and hypercarbia, some ventilatory responses and the breathing pattern during sleep are controlled by higher cerebral centers.^{8,9} The large number of apneic episodes noted during sleep by Rees et al.⁵ among diabetics with AN could indicate damage of the higher cerebral centers which, in turn, would explain the increased sensitivity of these patients to respiratory depressant drugs. After thorough investigation of a patient with repeated severe hypoglycemic episodes Boden et al.²⁶ also arrived at a similar conclusion, namely, that in diabetics with long-standing disease hypothalamic damage could account for the inappropriate responses of the counterregulatory hormones to hypoglycemia. On the other hand, following the autopsy of two diabetic patients with AN who died unexpectedly, Ewing and his colleagues²⁷ felt that an abnormal autonomic reflex mechanism was the most likely cause of

death, accounting for the lack of a discernible cause at autopsy. Indeed, a strong central inhibition of breathing and respiratory arrest can result from stimulation of the upper airways²⁸ and it is possible that some mechanism, such as aspiration of gastric contents, could trigger off this or a similar reflex in diabetics with AN with fatal consequences.

In conclusion, autonomic neuropathy is an irreversible condition^{4,11} with disabling symptoms and carries a poor prognosis. The disease has various manifestations, but we have not found any evidence to indicate that autonomic neuropathy is associated with defective ventilatory responses to hypoxemia or to hypercarbia.

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