Increased Sympathetic Outflow in Cirrhosis and Ascites: Direct Evidence from Intraneural Recordings

John S. Floras, MD, DPhil; Louis Legault, MD; Gilles A. Morali, MD; Kazuhiro Hara, MD; and Laurence M. Blendis, MD

Objective: To determine if central sympathetic outflow is increased in patients with cirrhosis and ascites.

Patients: Eleven patients with cirrhosis and ascites, 8 patients with cirrhosis but without ascites, and 7 age-matched and 8 young healthy volunteers.

Methods: With subjects supine, direct microneurographic recordings of efferent post-ganglionic muscle sympathetic nerve activity were obtained from the peroneal nerve, and sympathetic burst frequency was compared with subjects' blood pressure, heart rate, sodium excretion, catecholamines, and plasma renin activity. All patients with cirrhosis were studied at least 5 days after withdrawal from all medications and after 7 days of a 20 mmol/d sodium, 1-L fluid-restricted diet. Age-matched volunteers were studied after 7 days of 20 mmol/d sodium intake and young healthy volunteers after 7 days of 150 mmol/d sodium intake.

Results: Sympathetic nerve activity in ascitic patients (65 ± 15 bursts/min; mean ± SD) was markedly increased, whether compared with patients with cirrhosis but without ascites (34 ± 16 bursts/min; P < 0.001), age-matched healthy volunteers on similar sodium intake (27 ± 22 bursts/min; P < 0.001), or young healthy subjects (21 ± 10 bursts/min; P < 0.001). The frequency of muscle sympathetic nerve discharge was directly related to plasma norepinephrine and epinephrine concentrations, plasma renin activity, and heart rate, all of which were increased in those patients with cirrhosis and ascites, and inversely related to 24-hour urinary sodium excretion, the fractional excretion of sodium, and subjects' pulse pressures. Sympathetic nerve activity fell from 78 to 6 bursts/min in one patient after liver transplantation.

Conclusions: This study provides the first direct evidence that elevated plasma norepinephrine concentrations in patients with cirrhosis and ascites are due to increased central sympathetic outflow. Sympathetic nerve activity is not increased in patients with cirrhosis but without ascites. Because there were direct positive correlations of sympathetic nerve activity with plasma norepinephrine concentrations, plasma epinephrine concentrations, plasma renin activity, and heart rate, the increase in central sympathetic outflow in patients with cirrhosis and ascites appears generalized and not restricted to muscle nerves. The anti-natriuretic effects of parallel increases in renal and muscle sympathetic nerve activity could account for the inverse correlation between muscle sympathetic nerve activity and sodium excretion.

It has been postulated that increased sympathetic activity in cirrhotic patients with ascites may contribute to their impaired sodium and water excretion. It has been postulated that increased sympathetic activity in cirrhotic patients with ascites may contribute to their impaired sodium and water excretion. Plasma norepinephrine concentrations are increased in such patients. This is due to a decreased clearance rather than to greater norepinephrine spillover into plasma. The radiotracer kinetic technique used in such studies (1-5), however, quantitates the rate at which neuronally released norepinephrine appears in plasma, not the rate of release of norepinephrine from sympathetic nerve endings nor sympathetic nerve traffic. The elevated rate of appearance of norepinephrine in these patients could also result from decreased norepinephrine extraction within the neurovascular junction, decreased pre-junctional alpha-2-adrenoreceptor-mediated inhibition of norepinephrine release, or an enhanced pre-junctional modulation of neurotransmitter release by epinephrine (7-10) and angiotensin (7, 11, 12). Patients with decompensated cirrhosis and ascites display generalized activation of their sympathetic nervous and renin-angiotensin axes (1-5, 13, 14), suggesting an alternative mechanism to increased sympathetic neural outflow that could account for the elevated rate of norepinephrine spillover into plasma.

To overcome the limitations of this indirect method of assessing sympathetic tone, and to resolve this ambiguity, we used the microneurographic technique (15) to record sympathetic nerve activity directly from the peroneal nerves of patients with cirrhosis and ascites and, for comparison, from healthy volunteers. Our principal objective was to determine whether central sympathetic outflow is increased in cirrhotic patients with ascites and, if so, whether the neurohumoral and hemodynamic status of these patients was related to their sympathetic nerve activity. A secondary objective was to determine whether the impaired sodium excretion of patients with cirrhosis was also related to increased central sympathetic outflow.

Patients and Methods

Nineteen patients with biopsy-proven cirrhosis were studied: eleven patients with ascites refractory to aggressive medical management (20-mmol sodium, 1-L fluid diet; 400 mg spironolactone or 30 mg amiloride and more than 80 mg furosemide daily) (7 men and 4 women, aged 53 ± 11 years; mean ± SD) and 8 patients (6 men and 2 women, aged 54 ± 11 years) with cirrhosis but without ascites on abdominal ultrasonography (Table 1). The cause of cirrhosis in the 11 patients with ascites was alcoholic in 6 patients; post-necrotic in 4; and cryptogenic in 1. The cause in the 8 patients without ascites was alcoholic in 6 patients; post-necrotic in 1; and idiopathic micronodular in 1 patient. Patients with clinical evidence of autonomic neuropathy, diabetes, or left ventricular dysfunction were excluded. Cirrhotic patients were hospitalized in our Clinical Investigati-
### Table 1. Comparison between Patients with Cirrhosis and Normal Subjects

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<td>71 ± 8</td>
<td>49 ± 10</td>
<td>60 ± 10‖</td>
<td>21 ± 10§</td>
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* 3b = post-liver transplantation (data excluded from calculation of mean values).
† NA = not available.
‡ P < 0.05 compared with patients with cirrhosis and ascites.
§ P < 0.001 compared with patients with cirrhosis and ascites.
‖ P < 0.01 compared with patients with cirrhosis and ascites.

Subjects were studied supine in the post-absorptive state. An indwelling intravenous catheter, placed in a right forearm vein, was used for blood sampling. Blood pressure was measured every minute by an automatic cuff recorder (Physio-Control Lifestat 200; Redmond, Washington). Respiratory excursions were measured continuously by a pressure transducer and recorded simultaneously with the heart rate, electrocardiogram, and sympathetic neurogram on an 8-channel ink recorder.

Post-ganglionic multifiber sympathetic nerve activity was recorded from a muscle fascicle of the peroneal nerve posterior to the fibular head. Methods used to obtain a mean voltage neurogram, evidence that the intermittent, pulse-synchronous discharge recorded in the neurogram represents efferent post-ganglionic sympathetic activity, and the criteria that distinguish

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...tigations were approved by our institutional Human Subjects Review Committee. Informed written consent was obtained from all subjects.

Fifteen healthy volunteers who were not taking any medication were also studied. These subjects were not hospitalized. Seven of these (5 men, 2 women) were matched by age (43 ± 16 years) with patients with cirrhosis and ascites and were also placed on a 20 mmol/Sodium restricted diet. The other 8, all men (aged 28 ± 4 years), were prescribed a 150 mmol sodium intake to begin 7 days before their study. On the study day both the patients and the normal subjects on the 20 mmol sodium diet provided a 24-hour urine collection for determination of sodium excretion and creatinine clearance. The fractional excretion of sodium was calculated from the ratio of their sodium clearance and creatinine clearance. These investigations were approved by our institutional Human Subjects Review Committee. Informed written consent was obtained from all subjects.

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Table 1. (Continued)

<table>
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<tr>
<th>Muscle Sympathetic Nerve Activity</th>
<th>Plasma Norepinephrine bursts/100 heart beats</th>
<th>Plasma Epinephrine nmol/L</th>
<th>Plasma Renin Activity ng/L - s</th>
<th>Urinary Sodium Excretion nmol/d</th>
<th>Creatinine Clearance mL/s</th>
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79 ± 13 7.1 ± 4.8 1.3 ± 1.0 4.5 ± 2.3 3.80 ± 3.34 1.19 ± 0.45 0.04 ± 0.04

39 NA NA 0.2 18 0.73 0.17
51 NA NA 0.3 21 1.12 0.13
87 1.5 0.1 1.1 38 1.00 0.34
22 NA NA 0.2 21 2.00 0.15
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51 3.0 0.1 1.9 69 3.20 1.34 0.06
80 4.4 NA 6.1 1.34 0.06
81 8.6 NA NA NA NA NA
53 ± 32 1.5 ± 0.52 0.7 ± 1.2 0.4 ± 0.35 33.75 ± 9.75$ 1.38 ± 0.46 0.22 ± 0.10$

25 2.3 0.2 0.3 18 1.08 0.13
91 3.3 0.2 0.6 14 1.15 0.10
78 2.4 0.1 0.9 41 1.11 0.23
13 1.8 <0.1 0.2 34 1.10 0.26
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9 1.6 <0.1 0.6 69 2.30 0.25
39 ± 32 2.4 ± 0.72 <0.2 ± 0.14 0.7 ± 0.55 32.00 ± 21.12$ 1.36 ± 0.48 0.18 ± 0.08$

39 ± 32 2.4 ± 0.72 <0.2 ± 0.14 0.7 ± 0.55 32.00 ± 21.12$ 1.36 ± 0.48 0.18 ± 0.08$

28 1.2 0.4 0.7 NA NA NA
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34 1.9 <0.1 0.7 NA NA NA
44 1.6 <0.1 0.2 NA NA NA
31 0.8 <0.1 <0.1 39 0.3 0.3 0.3 30 1.50 0.17
15 1.8 <0.1 0.2 NA NA NA
33 ± 32 1.4 ± 0.71 <0.2 ± 0.1 0.4 ± 0.2$ NA NA NA

After a 10- to 15-minute stabilization period, sympathetic nerve activity, blood pressure, and heart rate were recorded during 10 to 20 minutes of quiet rest. Mean values for this period are reported. Venous blood was withdrawn for plasma catecholamine and renin determinations.

Data are expressed as mean ± SD. A one-way ANOVA was used for between-group comparisons. Correlations between sympathetic nerve activity and other variables were calculated using the Pearson correlation coefficient.

### Results

#### All Subjects

Muscle sympathetic nerve activity, plasma norepinephrine and epinephrine concentrations, plasma renin activity, and heart rate were all increased in patients with cirrhosis and ascites, whether compared with patients with cirrhosis but without ascites or with normal subjects (Table 1). In some patients with ascites, virtu-
Figure 1. Neurograms. Upper Panel. Mean voltage neurogram for muscle sympathetic nerve activity (SNA) and the electrocardiogram (ECG) in Subject 3, before (left) and after (right) successful liver transplantation. Before transplantation, virtually all cardiac cycles are associated with a sympathetic burst; after transplantation, sympathetic nerve activity is infrequent. Lower Panel. Mean voltage neurogram of muscle sympathetic nerve activity (SNA) and the electrocardiogram (ECG) in Subject 5 (patient with refractory ascites) and age-matched Subject 33 (normal subject).

ally every cardiac cycle was associated with a burst of sympathetic activity (Figure 1, Table 1), a pattern almost never seen in normal subjects. The increased burst frequency could not be attributed to the faster heart rates of patients with ascites because their sympathetic burst incidence was also significantly elevated (Table 1). Figure 1 (lower panel) compares sympathetic neurograms from a patient with ascites and an age-matched healthy subject.

Comparison of sympathetic nerve activity with other study variables in the 34 subjects overall identified several positive correlations. Sympathetic burst frequency was directly related to (log) plasma norepinephrine concentrations (r = 0.72; P < 0.001; n = 32), (log) epinephrine concentrations (r = 0.55; P < 0.005; n = 30), (log) plasma renin activity (r = 0.77; P < 0.001; n = 34), and heart rate (r = 0.63; P < 0.001; n = 34) (Figure 2). There was a strong positive correlation between (log) plasma norepinephrine concentrations and (log) plasma renin activity (r = 0.74; P < 0.001; n = 32).

The arterial and pulse pressures of patients with cirrhosis and ascites did not differ from patients with cirrhosis but without ascites, or from values recorded in both groups of normal subjects (Table 1). There were no significant correlations between sympathetic nerve activity and systolic, mean, or diastolic blood pressure in the 34 subjects overall, but more frequent sympathetic discharge was evident in subjects with narrower pulse pressures (r = -0.35; P < 0.04).

The 24-hour urinary sodium excretion and the fractional sodium excretion of patients with cirrhosis and ascites were markedly reduced, as compared with both nonascitic cirrhotic patients and the sodium-restricted normal subjects. Creatinine clearance, on the other hand, was similar in all three groups (Table 1). Overall, there were significant inverse correlations between sympathetic burst frequency and (log) 24-hour urinary sodium excretion (r = -0.64; P < 0.001; n = 24), (log) fractional sodium excretion (r = -0.56; P < 0.005), and creatinine clearance (r = -0.43; P < 0.04).

The two groups of control subjects had similar heart rates, sympathetic burst frequencies and burst incidences, and plasma epinephrine concentrations and plasma renin activity, but plasma norepinephrine concentrations were higher in the older, sodium-restricted subjects (P < 0.02).

The effect on sympathetic nerve activity of the Valsalva maneuver was studied in five normal subjects and five patients with ascites. In the normal subjects, sympathetic nerve activity fell from 44 ± 13 bursts/min during the strain phase of the Valsalva maneuver to 16 ± 7 bursts/min in the 20-s period immediately after Valsalva (P < 0.05). Release of the Valsalva maneuver did not suppress sympathetic nerve activity in the five patients with ascites (Figure 3).

Patients with Cirrhosis

Muscle sympathetic nerve activity was not increased above control values in the eight patients with cirrhosis but without ascites. In addition, values for heart rate, plasma norepinephrine, plasma epinephrine, and plasma renin activity were not increased in these patients, whether compared with the older subjects on restricted sodium intake or the younger subjects ingesting 150 mmol sodium per day.

When we compared the sympathetic nerve activity with indices of neurohumoral activation in these 19 patients with cirrhosis, we again identified several positive correlations. Sympathetic burst frequency was directly related to (log) plasma norepinephrine concentrations (r = 0.73; P < 0.001; n = 17), (log) plasma renin
activity (r = 0.80; P < 0.001; n = 19), and heart rate (r = 0.75; P < 0.001; n = 19). We found no significant correlations between sympathetic nerve activity and systolic, mean or diastolic blood pressure in these patients with cirrhosis but found more frequent sympathetic discharge in those patients with narrower pulse pressures (r = −0.51; P < 0.03; n = 19).

Both the (log) 24-hour urinary sodium excretion (r = −0.65; P < 0.005; n = 18) and (log) fractional sodium excretion (r = −0.56; P < 0.02) were inversely correlated with the sympathetic burst frequency of the cirrhotic patients. The correlation between sympathetic nerve activity and creatinine clearance (r = −0.43) was not significant.

Sympathetic nerve activity fell from 78 to 6 bursts/min and norepinephrine from 7.1 to 0.2 nmol/L in the one patient with refractory ascites studied shortly before, and 1 month after, successful liver transplantation (Table 1).

Discussion

This microneurographic study provides the first direct evidence for increased central sympathetic outflow in patients with cirrhosis and ascites. In contrast, sympathetic nerve activity was not increased in those patients with cirrhosis but without ascites. Our mean values for muscle sympathetic nerve activity in these patients with ascites are similar or greater than those levels of sympathetic burst frequency documented in patients with congestive heart failure (18). In some patients, virtually every cardiac cycle was associated with a burst of sympathetic activity. A burst incidence of this magnitude is not seen in normal subjects (15-18, 21-28).

The potential effects of age and dietary sodium restriction on sympathetic nerve activity of normal subjects are modest (18, 21, 22, 26, 27) and cannot explain the threefold higher sympathetic burst frequency in patients with ascites (65 ± 15 bursts/min) than in the young healthy volunteers ingesting 150 mmol of sodium daily (21 ± 10 bursts/min; P < 0.001). Similarly low levels of muscle sympathetic discharge were recorded in the older, sodium-restricted normal subjects (27 ± 22 bursts/min).

The concept that sympathetic activity is increased in patients with cirrhosis and ascites is not novel; several groups have reported increased norepinephrine spillover in such patients (3, 5). The radiotracer technique, however, has several limitations. It quantitates the appearance of norepinephrine in plasma, not the rate of norepinephrine release.
epinephrine release or sympathetic nerve activity; it lacks the sensitivity needed to detect abrupt changes in sympathetic outflow, as with the Valsalva maneuver; and it does not permit definitive conclusions as to the mechanism responsible for the increased norepinephrine spillover documented in these patients. The microneurographic technique overcomes these limitations: Our data indicate that central sympathetic outflow is indeed increased in patients with cirrhosis and ascites. The lack of sympatho-inhibition in response to the release of the Valsalva maneuver also suggests that the high sympathetic nerve activity in patients with ascites is relatively resistant to reflex suppression.

Although the microneurographic technique can only be applied to nerves accessible percutaneously, that is, muscle or skin (15), significant positive correlations in this study between sympathetic burst frequency and plasma norepinephrine and epinephrine concentrations, plasma renin activity, and heart rate suggest that sympathetic traffic is diffusely increased in patients with ascites, involving cardiac, renal and adrenal, as well as muscle sympathetic nerves. Sympathetic nerve activity, heart rate, plasma norepinephrine and epinephrine concentrations, and plasma renin activity were elevated in the patients with decompensated cirrhosis with ascites but were not increased above control values in patients with cirrhosis but without ascites.

Several groups have shown that the rate of release of norepinephrine by the kidney is increased in patients with ascites and have attributed this observation to increased efferent renal sympathetic nerve discharge (1, 4, 5, 29). Efferent renal sympathetic nerve activity is also increased in rats with experimental hepatic cirrhosis caused by common bile duct ligation and fails to suppress normally in response to an isotonic saline load (30). Stimulation of renal sympathetic nerves increases renal tubular sodium re-absorption both by activation of the renin-angiotensin system and through tubular mechanisms (31-33). Just as the increased renal efferent sympathetic nerve activity of cirrhotic rats contributes to their inability to excrete an isotonic saline load (30), an increase in renal sympathetic traffic, in parallel with their enhanced muscle sympathetic outflow, could contribute to the renal sodium retention of patients with cirrhosis and ascites (1-5, 34, 35). Indeed, a natriuretic and diuretic response to bilateral lumbar sympathetic block (to produce selective bilateral renal denervation) has been documented in patients with refractory ascites and avid sodium retention (36).

The significant positive correlation between muscle sympathetic nerve activity and plasma renin activity in our subjects is consistent with the concept that renal sympathetic nerve activity is also increased in patients with cirrhosis and ascites. We would suggest that the significant inverse correlations between sympathetic burst frequency and both the fractional excretion of sodium and 24-hour urinary sodium excretion reflect parallel and quantitatively similar increases in muscle and renal sympathetic nerve activity in such patients. Because renal denervation reverses the blunted natriuretic and diuretic responses to atrial natriuretic factor in cirrhotic rats (37), an increase in sympathetic traffic to the kidney could also explain an observation in one of our earlier studies, namely, that many patients with cirrhosis and ascites are resistant to the natriuretic effects of this peptide (38).

Arterial and pulse pressure, two stimuli to arterial baroreceptor discharge (39), were virtually identical in patients with cirrhosis and ascites, cirrhosis without ascites, and the two groups of normal subjects, yet there was an inverse correlation overall between sympathetic burst frequency and pulse pressure. This observation is of interest, because the increased central sympathetic outflow recorded in these patients with ascites could be considered an appropriate reflex response to hypovolemia, that is, withdrawal of afferent baroreceptor input. Our finding of increased sympathetic outflow in association with elevated plasma catecholamines, renin activities, and heart rates in patients with ascites is also consistent with this concept. Nonetheless, whether the increased neurohumoral drive of patients with cirrhosis and ascites is caused by decreased effective circulatory blood volume with secondary renal sodium retention (“underfilling”) or is caused by activation of a sympatho-excitatory hepato-renal reflex resulting from increased intra-hepatic sinusoidal pressure...
(primary renal sodium retention, or "overflow") remains a major area of controversy (14, 34, 35, 40-42) that is not resolved by these experiments.

In normal subjects, small increases in central venous pressure have marked inhibitory effects on muscle sympathetic nerve activity whereas small decreases in central venous pressure elicit marked increases in muscle sympathetic nerve activity (24, 25). We explored the effect on sympathetic nerve activity of release of the Valsalva maneuver, which redistributes blood volume into the central and arterial compartments. A more definitive study of the contribution of volume-sensitive cardiac vagal afferents as well as arterial baroreceptor afferents (14, 35) to the increased sympathetic outflow of these patients with ascites would require careful, invasive quantitation of central and systemic arterial pressure during such maneuvers. Without such measurements, we cannot exclude the possibility that the presence of portal hypertension and ascites diminishes the magnitude of the reflex sympatho-inhibitory stimulus on release of the Valsalva maneuver.

Sympathetic nerve activity and plasma norepinephrine and plasma epinephrine concentrations all fell in the one patient studied after hepatic transplantation to values below even those recorded in our control subjects. Because of the internal consistency of these observations, the reduction in nerve activity cannot be attributed simply to differences in electrode placement and, although this was the only patient in whom serial recordings were made, we should point out that the within-subject variability of muscle sympathetic nerve activity has been well established (17) and is quite small—about 9%—when repeated recordings are made with intervals of 3 weeks to 21 months between studies. If increased hepatic sinusoidal mechanoreceptor discharge does contribute reflexly to the increased sympathetic outflow in patients with ascites ("hepato-renal reflex") (35, 40, 41), one interpretation of these observations in this single patient is that this excitatory stimulus must be diffuse and not specific to the kidney, because muscle sympathetic nerve activity, plasma norepinephrine, heart rate, and plasma epinephrine concentrations were all elevated in this patient (as in the group with ascites as a whole) and were substantially lower after hepatic transplantation. This interpretation would be consistent with results of animal experiments demonstrating that activation of hepatic baroreceptors causes reflex increases in both renal and cardiac sympathetic nerve activity—increases that can be abolished by hepatic denervation (40). Another interesting point is that this patient was taking 800 mg per day of cyclosporine at the time of his second study after transplantation. His sympathetic nerve activity was even lower than that recorded in our normal subjects, a finding that is inconsistent with the recently published hypothesis that cyclosporine increases muscle sympathetic nerve activity in humans (28).

Liver disease of this severity is often associated with muscle wasting and autonomic neuropathy (43). Such changes cannot account for the much higher efferent muscle sympathetic nerve activity in our patients with ascites. Muscle sympathetic nerve discharge frequency is independent of the size of the innervated muscle group: Simultaneous recordings comparing muscle sympathetic nerve discharge to the arm and leg at rest have documented nearly identical activity (17, 44) and sympathetic nerve activity is diminished, absent, or technically impossible to record in patients with autonomic neuropathy.

The generalized neurohumoral activation seen in these patients with cirrhosis and ascites is comparable to that described in patients with congestive heart failure (14, 18) but the circulatory response to these vasoconstrictors is quite different: Patients with ascites tend to have an increased cardiac output (45) and do not display the peripheral vasoconstriction and inappropriately elevated afterload of patients with congestive heart failure. Evidence from several sources (46) indicates that the pressor response to these vasoconstrictors is blunted in patients with liver disease although the mechanism for this desensitization has not been clearly established. Indeed, one could argue that activation of the sympatho-adrenal and renin-angiotensin aldosterone systems in these patients is essential to maintain systemic vascular resistance and perfusion pressure and counter any predisposition to decreased effective arterial volume in such patients.

Our key findings are that central sympathetic outflow to muscle is increased in patients with cirrhosis and ascites and that sympathetic nerve activity is not increased in patients with cirrhosis but without ascites. The significant positive correlations between muscle sympathetic nerve activity and norepinephrine, epinephrine, renin, and heart rate suggest that the increased muscle sympathetic nerve activity of patients with ascites reflects a generalized increase in efferent sympathetic traffic. A parallel increase in muscle renal sympathetic nerve activity may contribute to the renal sodium retention and resistance to the atrial natriuretic factor that have been reported in many patients with ascites. We conclude that the high plasma norepinephrine concentrations seen in patients with cirrhosis and ascites are caused by increased sympathetic outflow.


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