

Impaired neurogenic control of skin perfusion in erythromelalgia.

Impaired Neurogenic Control of Skin Perfusion in Erythromelalgia

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Erythromelalgia is a clinical diagnosis characterized by erythema, increased temperature and burning pain in acral skin. The pain is relieved by cooling and aggravated by warming. The symptoms have been hypothesized to be caused by skin hypoxia due to increased arteriovenous shunting. We examined skin microvascular perfusion in response to vasoconstrictor and vasodilator stimuli, to characterize local and central neurogenic reflexes as well as vascular smooth muscle and vascular endothelial function, using laser Doppler perfusion measurements in 14 patients with primary erythromelalgia and healthy control persons. Skin perfusion preceding provocative stimuli was significantly reduced in patients with erythromelalgia ($p < 0.01$). The laser Doppler flowmetry signal after sympathetic stimulation of reflexes mediated through the central nervous system, was significantly diminished in patients with erythromelalgia as compared with healthy controls (Valsalva's maneuver $p < 0.01$; contralateral cooling test $p < 0.05$). Local neurogenic vasoconstrictor (venous cuff occlusion and dependency of the extremity) and vasodilator reflexes (local heating of the skin), as well as tests for vascular smooth muscle and vascular endothelial function (postocclusive hyperemic response) were maintained. These results indicate that postganglionic sympathetic dysfunction and denervation hypersensitivity may play a pathogenetic role in primary erythromelalgia, whereas local neurogenic as well as endothelial function is unaffected.

Erythromelalgia is a condition characterized by burning extremity pain, aggravated by warming and relieved by cooling, erythema, and increased temperature of affected skin. The symptoms and findings are most often intermittent and often absent during physical

examination (Thompson et al, 1979). In most textbooks erythromelalgia is considered to be a separate disease entity, whereas others have proposed that the condition represents a symptom complex caused by a specific pathophysiologic response, microvascular arteriovenous shunting (Kvernebo, 1998). This is analogous to the view that inflammation is not one single disease, but a physiologic response to stimuli such as infection, trauma, or tumor. According to the shunting hypothesis, symptoms are caused by tissue hypoxia, induced by a maldistribution of skin microvascular blood flow with increased thermoregulatory flow through shunts and a corresponding deficit in nutritive perfusion.

There are few studies on pathogenetic mechanisms in erythromelalgia. Dysfunction of autonomous nervous function has been demonstrated (Sandroni et al, 1999), and disturbances in the regulation of microvascular perfusion have also been documented (Littleford et al, 1999a; Mork et al, 2000). Littleford et al showed vasoconstriction in asymptomatic erythromelalgia between hyperemic attacks, whereas our group published results in favor of the shunting hypothesis in symptomatic patients. Distribution of blood flow is regulated by smooth muscle cell tone in arterioles and precapillary vessels. Smooth muscle cell tone is again influenced by the metabolic state of the tissue, neurogenic, and endothelial activity, as well as the transmural hydrostatic pressure. In this study laser Doppler perfusion measurements have been used to assess change in skin microvascular perfusion in response to vasoconstrictor as well as vasodilatory stimuli. The aim was to characterize local and central neurogenic, as well as endothelial cell function in erythromelalgia, as compared with healthy controls.

MATERIALS AND METHODS

Study Population

Since 1983 we have systematically studied erythromelalgia patients. A review of clinical and epidemiologic findings in 87 patients has previously been published (Kalgaard et al, 1997). In this study, we selected patients from our database according to the following criteria: primary adult erythromelalgia patients (no known underlying disease, age > 18 y) and severity group 2 or 3 (Kalgaard et al, 1997). Erythromelalgia severity group 2 implies that the patient feels uncomfortably warm periodically and cools the feet by walking barefoot on cold floors, etc. Group 3 indicated periods of burning pain and active cooling of the feet in cold water for less than 1 h a day. Subjects were not included if they had a history of any disease or condition that in the opinion of the investigator could interfere with the results of the study, use of vasoactive drugs at the time of study or within the previous 3 mo, or drug or alcohol abuse. The erythromelalgia patients were compared with sex- and age-matched volunteers enrolled from the hospital staff. Procedures and purpose of the examinations were fully explained to all participants, who gave their written, informed consent. The Regional Ethical Committee approved the study.

Laser Doppler perfusion measurements

The principles of laser Doppler perfusion measurements have been described in detail elsewhere (Nilsson et al, 1980). This method assesses cell flux as the product of a number of blood cells and mean blood cell velocity in a measuring volume of a few cubic millimeters. The equipment used in this study was noninvasive and capable of

recording dynamic alterations in skin perfusion. A low power (2 mW) He-Ne laser beam operating at a wavelength of 632.8 nm (Periflux PF2, Perimed AB, 517526 Jarfilla, Sweden) was used. A bandwidth filter of 12 kHz, an output circuit time constant of 0.2 s and a chart recording speed of 75-150 mm per min were employed. The flowmeter output signal was recorded with a linear yen recorder, and expressed in arbitrary flux units. Prior to examination, the technical zero level was obtained by placing the probe against a white reflecting surface. The biologic zero, the flux value recorded in the skin after cuff occlusion, was less than 5% of baseline perfusion and was not subtracted from the recorded values. The recorded curves showed fluctuations, but it was possible to estimate visually the mean laser Doppler perfusion measurement levels for a quantitative comparison.

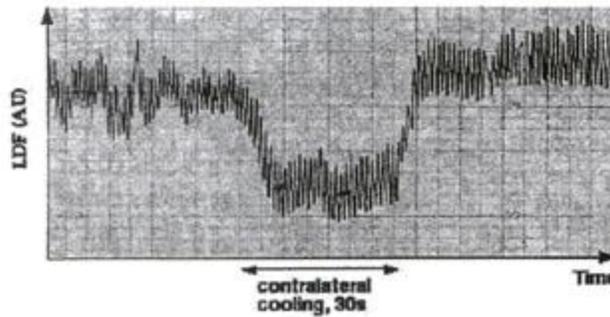


Figure 1. Laser Doppler signal at the pulp of the first toe, showing the vasoconstrictor response to indirect cooling in a control subject. The first part of the curve shows pulse synchronous microvascular perfusion before cooling given in arbitrary units (AU). During contralateral cooling, perfusion is reduced about 50%.

Perfusion tests

Laser Doppler perfusion measurement assessments of skin perfusion were performed at the pulp of the first toe at rest and during physiologic provocations. The following tests were chosen.

Perfusion response to Valsalva's maneuver Valsalva's maneuver induces an abrupt decrease in venous return to the heart and provokes skin vasoconstriction by sympathetic activation. The afferent pathway in this centrally controlled (spinal) reflex is stimulated through arterial and cardiac low-pressure receptors and the efferent limb induces skin vasoconstriction (Khan et al, 1991; Low, 1997; Morris and Gibbins, 1997).

Perfusion response to contralateral cooling (Fig 1) This test measures the skin vasoconstrictor response to cooling of the contralateral extremity with its pathway through the spinal cord (Khan et al, 1991; Low, 1997; Morris and Gibbins, 1997). The contralateral cold stimulus appears to be the maneuver that most consistently evokes a vasoconstrictory response (Low et al, 1983).

Perfusion response to dependency or cuff-induced venous stasis Cuff induced venous stasis or shifting a leg to a gravity-dependent position provokes a physiologic skin

vasoconstrictive response activated by increased transmural venous pressure. The receptor is situated in venules whereas the effector is the arteriole. These venoarteriolar reflexes are local peripheral sympathetic reflexes with retrograde impulses in the axonal postganglionic fibers (Vissing et al, 1997). They aid in the transient maintenance of postural normotension and reduce the orthostatic increase in tissue fluid by adjusting precapillary to postcapillary resistance ratio (Melandar et al, 1964; Henriksen, 1976; Morris and Gibbins, 1997).

Perfusion response to cuff induced ischemia (Fig 2)

The hyperemia following transient ischemia is dependent on several mechanisms. The reduced transmural pressure caused by cuff inflation leads to decreased tone in the arterioles.

When the cuff is released, the transmural pressure increases towards preocclusive levels, causing vascular smooth muscle contraction. Vasodilatation beyond this initial phase is dependent on a functionally intact endothelium (Tagawa et al, 1994; Andreassen et al, 1995).

Increased flow and shear stress exposed to the endothelium promotes release of nitric oxide from the endothelial cell causing continued vasodilatation in the mid-to-late phase of the response. Consequently, this part of the response can be used as an indicator of endothelial function. In this study, vascular smooth muscle function during postocclusive hyperemia was quantified as the percentage reduction in flux 5 s after peak flow. The endothelial capacity for the production and release of vasodilatory substances were estimated according to the capacity for maintaining hyperemia 45-75 s after peak flow (mid-to-late phase of the response).

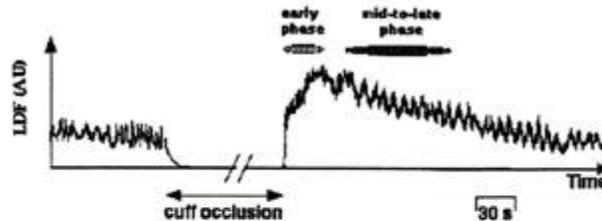


Figure 2. Laser Doppler signal at the pulp of the first toe before, during, and after a 3 min thigh cuff occlusion in a control subject. The first part of the curve shows pulse synchronous microvascular perfusion at baseline, given in arbitrary units (AU). During cuff occlusion, perfusion is reduced towards zero. Following cuff deflation, the early phase of the hyperemia is determined by blood inflow capacity and vascular smooth muscle response to regain of transmural pressure in the arterioles. A persistent hyperemia in mid-to-late phase is dependent on the capacity of the vascular endothelium to produce and release vasodilatory substances.

Perfusion response to local skin heating Local application of heat evoke a hyperemic response. This vasodilatation is a local axon reflex mediated by mechano-insensitive nociceptive C fibers (Schmelz et al, 2000). The function of this reaction is tissue protection by enhanced thermal dilution when the tissue is exposed to temperatures a few degrees above core temperature. Under comfort ambient temperature conditions this axon reflex is not related to sympathetic activity (Low et al, 1983; Magerl and Treede, 1996). The central control of microvascular thermoregulatory arteriovenous anastomoses is also unaffected (Bergersen et al, 1995).

Laboratory procedures

Subjects were instructed not to smoke or drink coffee, tea, or alcohol for a minimum of 12 h before the measurements. They were acclimatized in a supine position for 20 min in a quiet and draught-free environment with minimal audiovisual and mental stimuli.

The test site was uncovered prior to baseline flux measurements (Bircher et al, 1993). The room temperature was 23°C (22-24). Measurements were performed on the pulp of the first toe, a location where all patients in this study reported erythromelalgia symptoms.

For studies of the Valsalva's maneuver, subjects were asked to take a deep breath and then make a forced exhalation for 15 s against a closed glottis. Indirect cooling was performed by putting the contralateral foot into a cold water bath (temperature 15°C) for 30 s. Response to dependency was recorded with the leg in the supine and the vertical position. The difference in perfusion before and after inflation of a leg tourniquet to 50 mmHg for 30 s also demonstrated the venoarteriolar reflex. Postocclusive hyperemia was assessed with inflation of a thigh tourniquet to 280 mmHg for 3 min followed by a sudden pressure release of the cuff (Kvernebo et al, 1988). Finally, local thermal reactivity was assessed with a local thermostat probe (Perimed, Sweden) heated for 3 min to 28°C, 32°C, 36°C, 40°C, and 44°C, respectively.

Statistical analysis

Results were expressed as median with range in text and tables. Data were analyzed using chi square tests for demographic data, Mann-Whitney test for non-normal distributed data, and the ANOVA general lineal model test for repeated measurements, with Bonferroni correction for multiple comparisons. For correlations, the Pearson's linear and Spearman rank correlation tests were used. All significance levels reported were two-tailed, and $p \leq 0.05$ was considered statistically significant. All analyses were performed using SPSS 9.0 software (SPSS Inc., Chicago, IL).

Table I. Subject characteristics

	Erythromelalgia	Control subjects				
		Baseline	Valsalva CC ^d	VAR ^e VO ^f	POH ^g	Local heating
Female/male ^a	10/4	12/6	8/4	9/4	4/10	8/3
Age ^b	55 (17-74)	38 (26-79)	38 (26-60)	38 (26-69)	32 (24-75)	38 (29-58)
Duration ^c	10 (2-38)					
Severity ^c	2.6 (1.3-3.8)					

^aNumber related to sex.

^bYears, median with range.

^cConcurrent erythromelalgia severity group based on the need of cooling described in a scale from one (minimal symptoms) to eight (maximal symptoms), median with range.

^dContralateral cooling, response to indirect cooling.

^eVenoarteriolar reflex, response to dependency.

^fVenous occlusion, response to cuff induced venous stasis.

^gPostocclusive hyperemia, response to cuff induced ischemia

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h primary erythromelalgia fulfilling the inclusion and exclusion criteria were studied (Table 1). The concurrent severity of erythromelalgia was based on the mean value of the self-reported cooling score for 4 wk prior to measurements. None of the subjects had a history of cardiovascular or other serious diseases and did not use any vasoactive medication. No erythromelalgia patients had symptoms at the time of measurements. Before provocation, skin perfusion at the pulp of the first toe was significantly reduced in the erythromelalgia patients as compared with healthy control subjects ($p < 0.05$) (Table II).

The vasoconstrictor responses to Valsalva's maneuver ($p < 0.001$) and cold challenge

($p < 0.05$) were significantly attenuated in erythromelalgia patients compared with controls, with a high correlation between the two tests ($r = 0.76$, $p < 0.001$) (Table II). These results are in contrast to the vasoconstrictor responses to dependency and venous occlusion, where no statistical difference was demonstrated between the groups. A significant correlation between these tests was also found ($r_s = 0.38$, $p < 0.05$).

Local probe heating elicited significant skin vasodilatation in both groups. The increase in flux was significantly lower in erythromelalgia patients compared with the responses in control subjects ($p < 0.001$) (Fig 3).

The postocclusive hyperemic response, including the 45-75 s interval, did not differ statistically between the groups comparing repeated recordings at 10 s interval from 15 s post peak flow, although a nonsignificant trend to lower response was observed in the erythromelalgia group (Fig 4).

DISCUSSION

This study demonstrates that erythromelalgia patients without symptoms have a significantly lower skin perfusion during basal conditions than normal subjects. Vasoconstrictor responses involving central sympathetic reflexes were attenuated in erythromelalgia. Local neurogenic vasoconstrictor regulation, vasodilator response to local heating and hyperemic response to ischemia were maintained.

Erythromelalgia is a rare and heterogeneous condition. To minimize the problem of heterogeneity we defined pre-study inclusion and exclusion criteria. The patients fulfilling these criteria represent a subgroup of erythromelalgia patients, all primary cases with medium severity and duration of more than 6 y from onset of erythromelalgia symptoms. The patients were all asymptomatic during measurements.

The finding of reduced skin perfusion before provocation is in accordance with the clinical observations that many erythromelalgia patients exhibit cold acral skin and Raynaud's phenomenon between attacks. The finding also confirms that basal skin perfusion is reduced compared with healthy controls between erythromelalgia attacks using laser Doppler flowmetry (Littleford et al, 1999a). Using laser Doppler perfusion imaging, it was shown that there was a nonsignificant trend towards lower baseline perfusion in erythromelalgia patients (Mark et al, 2000). This vasoconstrictor tendency may be explained by enhanced vascular tone due to increased adrenergic vasomotor activity, adrenergic receptor hypersensitivity or malfunction of the endothelial production of vasoactive substances (endothelin, thromboxane A₂, nitric oxide, hyperpolarizing factors). Changes in microvascular architecture, such as reduced vascular density and perivascular edema, may also be

Table II. Baseline perfusion and vasoconstriction following Valsalva's maneuver and contralateral cooling are significantly reduced in primary erythromelalgia patients as compared with healthy controls

	Erythromelalgia	Control subjects
Baseline perfusion ^a	0.7 (0.2-12.8) ^f	4.7 (0.5-22.1)
Valsalva's maneuver ^b	34 (0-67) ^f	48 (32-80)
Contralateral cooling ^b	27 (0-80) ^g	48 (32-80)
Venoarteriolar reflex ^b	75 (29-92)	72 (16-96)
Venous occlusion ^b	60 (20-93)	54 (13-85)

^aBaseline perfusion given as relative flux units (RFU), median with total range.

^bVasoconstriction index defined as: $[(\text{Flux})_{\text{before stimulus}} - \text{Flux}_{\text{minimum after stimulus}}] / \text{Flux}_{\text{before stimulus}} \times 100\%$, median with range.

^f $p < 0.01$ as compared with control subjects.

^g $p < 0.05$ as compared with control subjects.

responsible. Abnormalities such as thickened blood vessel basement membranes, perivascular edema and endothelial swelling have been demonstrated in affected skin from a patient with erythromelalgia syndrome (Kvemebo, 1998). Arteriolar inflammation, fibromuscular intima proliferation, and thrombotic occlusions are typical skin biopsy results of erythromelalgia secondary to thrombocythemia (Michiels et al, 1985). On the other hand, with regard to capillary density of the affected skin, it has not been previously demonstrated that there was any difference among asymptomatic primary erythromelalgia patients (Asker et al in preparation).

Attenuated vasoconstrictor responses to Valsalva's maneuver and indirect cooling imply sympathetic nerve dysfunction. The sympathetic stimuli in these spinal reflexes activate different afferent pathways, but have common efferent pathways. Consequently, the findings are consistent with impaired postganglionic nerve function.

These data are in agreement with previous observations that demonstrated reduced vasoconstriction in response to inspiratory gasp and contralateral cold challenge in both primary and secondary erythromelalgia patients (Littleford et al, 1999b).

Histologic

evidence of decreased sympathetic innervation has been shown in skin from the dorsal aspect of the foot of three erythromelalgia patients (Uno and Parker, 1983; Vendrell et al, 1988; Staub et al, 1992). Two of these patients had diabetes mellitus and reduced nerve conduction velocities (Vendrell et al, 1988; Staub et al, 1992). Two patients with neuropathy in secondary erythromelalgia have been reported. Both had the combination of high levels of α -adrenergic sensitivity and reduced (X)-sympathetic nerve activity (Kitajima et al, 1985). Absence of vasoconstrictor response and presence of normal skin sympathetic traffic and normal somatoautonomic reflex arc by means of microneurographic recordings in a nerve trunk at a relatively proximal site in one patient with primary erythromelalgia have been published (Sugiyama et al, 1991). Distal length-dependent peripheral small fiber neuropathy, with selective involvement of cutaneous sympathetic fibers, has been demonstrated in patients with erythromelalgia and with lesser involvement of large nerve fibers (Sandroni et al, 1999). The beneficial effect of gabapentin reported in erythromelalgia further support the presence of impaired nerve function, as gabapentin is known to have some effect in neuropathy (Bonelli and Koltringer, 2000; Cohen, 2000). The dynamic nature of autonomic dysfunction may

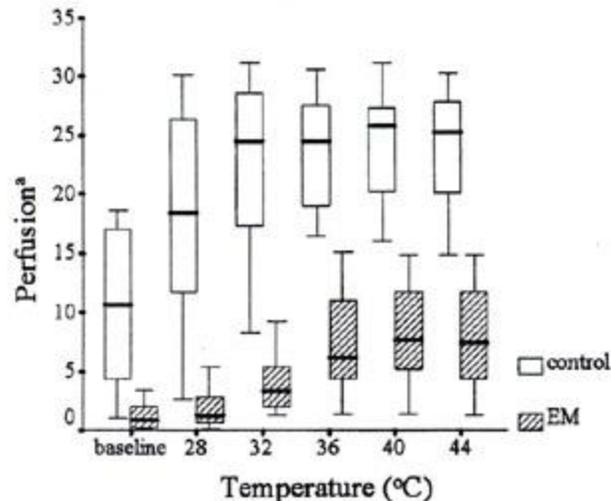


Figure 3. Local probe heating induced a significant vasodilatation in erythromelalgia patients and controls, but at a lower level in erythromelalgia patients. The increase in perfusion was significantly higher in controls compared with erythromelalgia patients ($p < 0.005$). Distribution of data is illustrated as box plots, where the boxes show the median with quartiles and extreme values. *Laser Doppler flux in arbitrary units (AU).

explain the fluctuations of the severity of erythromelalgia seen in many patients.

The intact venoarteriolar reflex and results from the venous occlusion test imply normal function of the local autonomic plexa and intact arteriolar smooth muscle function. These findings are consistent with the clinical observations that the patients in this study, and asymptomatic erythromelalgia patients in general, do not exhibit edema of affected skin.

Local heating is a stimulus for nociceptive C fibers in the local nerve plexa causing neurogenic vasodilatation. Skin perfusion in erythromelalgia patients did not reach control values, even at 44°C. This observation is consistent with

reduced vascular density, but intact nerve plexa function. Alternatively, the patients could have an intact microvascular structure, but a strong vasoconstrictor stimulus, maintained during local heating. In both circumstances, however, the dilatation of the local nociceptive C fibers was demonstrated. Hyperemic response to 44°C was also reduced in the erythromelalgia patients examined by Littleford et al. A structural microvascular angiopathy has previously been demonstrated in secondary erythromelalgia patients and in a case with erythromelalgic syndrome (Michiels et al, 1985; Drenth et al, 1996; Kvernebo, 1998).

The perfusion pattern following cuff occlusion shows an ability to maintain hyperemia' in the mid-to-late phase of the response in erythromelalgia patients, indicating intact endothelial capacity for production of dilatory factors (Tagawa et al, 1994; Andreassen et al, 1995). The perfusion values tended to be lower in patients, again compatible with reduced vascular density,

Our results are in accordance with previous findings of distal thin fiber neuropathy (Sandroni et al, 1999) and the postulation of denervation hypersensitivity (Uno and Parker, 1983; Kitajima et al, 1985; Littleford et al, 1999a, b). In a recent communication in this journal (Davis et al, 2004b; Mork and Kvernebo, 2000), erythromelalgia was discussed as a primary vascular or primary neurogenic condition. Previously, the existence of microvascular arteriovenous shunting in erythromelalgia was advocated and hypoxia in affected skin was demonstrated (Kvernebo, 1998). In this study we demonstrate an autonomic dysfunction in erythromelalgia. As hypoxia can lead to neuropathy and neuropathy can lead to maldistribution of blood flow with a

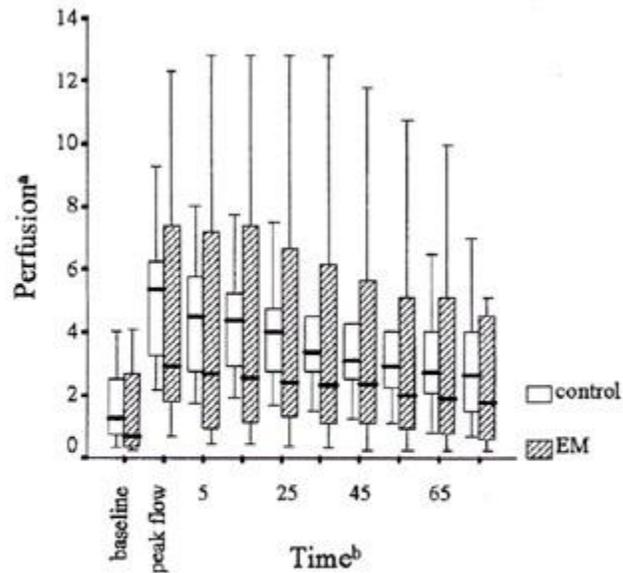


Figure 4. The hyperemic response after 3 min of arterial occlusion is intact in erythromelalgia patients. During analyses of each patient curve, the mean perfusion of 10 s periods was visually estimated. Distribution of data is illustrated as box plots, where the boxes show the median with quartiles and extreme values. *Laser Doppler flux in arbitrary units. ^bSeconds after peak flow.

corresponding hypoxia, it is not surprising that both microvascular perfusion disturbances and neurogenic dysfunction can be demonstrated in this patient group. Furthermore, many of the systemic diseases associated with secondary erythromelalgia (diabetes mellitus, connective tissue diseases, vasculitis, and cancer) induce both neuropathy and microvascular disorders (Kalgaard et al, 1997; Mork et al, 1999; Davis et al, 2000a).

In conclusion, these data demonstrate that asymptomatic patients with primary erythromelalgia have reduced cutaneous perfusion preceding provocation and impaired central sympathetic vasoconstrictor reflexes. Local autonomic reflexes and endothelial function are intact. Current findings provide support for the existence of efferent thin fiber neuropathy and denervation hypersensitivity. Further studies are needed to determine if erythromelalgia associated neuropathy is primary or secondary.

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