原 著

Comparison of Chronological Plot of RR Interval under Hypotensive Anesthesia: Effects of Trimetaphan, Nitroprusside and Nitroglycerin

Kumiko Taira*, Marie Ishihara*, Yukiko Mukubo*
Tomoko Fukada*, Kuniaki Otsuka*, Miwako Kawamata*

ABSTRACT

Purpose: To examine morphological changes in the chronological plot of RR intervals (RR interval trendgram, RR graph) and ΔRR/RR ratios (Δratio graph) under GOS anesthesia treated with trimetaphan compared to nitroprusside and nitroglycerin for induced hypotension.

Method: Twenty ASA I-II patients received trimetaphan (group T, n=10) or nitroprusside (group NP, n=10), and five ASA II patients with hypertension or ischemic heart disease received nitroglycerin (group NG, n=5). ECG records were measured before anesthesia (T0), before induced hypotension (T1), at 20 minutes after the hypotension (T2), and at 20 minutes after discontinuation of the hypotension (T3). A sequence of RR intervals were obtained from the ECG records with an electric caliper for 30 seconds, and the RR graphs and the Δratio graphs were plotted with a personal computer.

Results: The administration of trimetaphan significantly decreased the amplitude on the RR graph and the Δratio graph, under GOS anesthesia (at T2, $p < 0.05$ vs. T1). However, the administration of nitroprusside did not produce similar changes in the amplitude on the RR graph and the Δratio graph. In the T-NP groups the amplitude of RR graph decreased by induction of anesthesia (at T1, $p < 0.05$ vs. T0), but in the NG group the amplitude of RR graph did not decrease by induction of anesthesia.

Conclusion: Autonomic ganglion blocking by trimetaphan under GOS anesthesia reduces the amplitude on the RR graph and the Δratio graph.

Key words: RR interval, trimetaphan, nitroprusside, induced hypotension

INTRODUCTION

For anesthesiologists, heart rate variability (HRV) remains a mystery. This is due to the fact that we do not possess the knowledge of the morphological features of the chronological plot of RR interval (RR interval trendgram, in this study we named RR graph), over a short period of time, which is the most primitive representation of HRV. The results of a FFT analysis of the time serial RR interval data over a long time, obtained from ECG records, reveals there are small fluctuations in the high frequency spectrum power (HF: 0.15-0.4 Hz) and large fluctuations in the low frequency spectrum power (LF: 0.04-0.15 Hz). It is known that HF reflects parasympathetic activity, and LF or LF/HF reflects sympathetic activity[1~3]. Therefore, it is understandable that small waves of high frequency (2.5 to 6.7-second cycle) are found and larger waves of low frequency (6.7 to 25-second cycle) are found in the RR graph, displaying morp-

*Department of Anesthesiology, Tokyo Women's Medical University Second Hospital
**Department of Internal Medicine, Tokyo Women's Medical University Second Hospital

hological changes. It is also expected that the RR graph would show certain characteristic fluctuations corresponding to changes in cardiac autonomic activity.

In this study we investigated the effect of trimetaphan, the autonomic ganglion-blocker, on morphological changes in the time serial RR interval graph under GOS anesthesia. The aim of this study is to determine whether trimetaphan would suppress both small waves and larger waves on the RR graph. As the control, nitroprusside, the direct vasodilator, was set. Additionally, the data of nitroglycerin, the direct venous capacitance vessels dilator, was presented, which was administered to the patients with hypertension or ischemic heart disease to reduce blood pressure during anesthesia.

METHODS

Patients and Study Design

＜Trimetaphan Group and Nitroprusside Group＞

Twenty adult patients, ASA physical status I or II, scheduled for either an elective mastectomy or ENT surgery, were enrolled in the study after receiving informed consent approved by the local review board. Patients with cardiovascular, renal, diabetic, or neurological diseases or those taking antiarrhythmic agents were excluded. Patients were randomly assigned to receive either trimetaphan (n=10) or nitroprusside (n=10).

The ECG (BP508, Colin Co., Komaki, Japan) was monitored using standard limb leads (II). During anesthesia blood pressure was measured continuously with a noninvasive oscilometric device (BPM, Colin Co., Komaki, Japan). The mean arterial pressure (MAP) was determined with the blood pressure, when the amplitude of cuff pressure became the maximum value. A pulse oximeter (BP508, Colin Co., Komaki, Japan) was used throughout anesthesia.

The patients were premedicated with 50 mg of hydroxyzine i.m. at 30 min before the induction of anesthesia. Anesthesia was induced with 5 mg/kg of thiopental sodium i.v. followed by 0.1 mg/kg of vecuronium i.v. to facilitate tracheal intubation. The ventilation rate was adjusted to maintain the end-tidal CO_2 partial pressure between 30 to 35 mmHg, with a respiratory rate of 10 breath/min and an I/E ratio of 1:2. Anesthesia was maintained with 67% nitrous oxide and sevoflurane at end-tidal concentration of 1.7%, with an incremental dose of 1-2 mg of vecuronium for muscle relaxation, as required. End-tidal anesthetic concentrations were measured with an anesthetic gas monitor (BP508, Colin Co., Komaki, Japan).

Induced hypotension was started immediately after surgical incision. The infusion was started at a rate of 20 μg/kg/min trimetaphan or 0.5 μg/kg/min nitroprusside, and titrated until the MAP was 60-80 mmHg. Maintenance doses were administered until skin closure was started. The ECG was recorded on paper at a rate of 25 mm/sec for more than 30 sec for each case; and data was recorded before induction of anesthesia (T0), just before induced hypotension (just before skin incision, T1), at 20 min after administration of vasodilator infusion (T2), and at 20 min after discontinuation of vasodilator infusion (T3).

＜Nitroglycerin Group＞

Five patients with hypertension or ischemic heart disease, ASA physical status II, scheduled for either an elective mastectomy, ENT surgery, or laparocholecystectomy were enrolled in the study after receiving informed consent approved by the local review board. Four of them were medicated with calcium channel blocker and/or ACE antagonist, and the drugs were not discontinued before surgery.

They were administered nitroglycerin for controlling blood pressure during the operation. The methods used for monitoring anesthesia, the protocols of anesthesia, and the recording procedure of the ECG were identical to trimetaphan/nitroprusside groups.

ANALYSIS

For each case, a 30 sec segment of cardiac arrhythmia-free data was extracted. Electrocardiographic RR intervals were measured manually with an electronic caliper (accuracy: max deviation 0.02 mm over 100 mm, EAGLE 05.37005, Brown & Sharp, France), and data was stored in the personal computer (PC7DC7-GP0481C00, HITACHI, Tokyo, Japan).

The difference between two consecutive RR intervals was referred to as ΔRR. The ratio of ΔRR to RR was referred as Δratio. The chronological plot of RR intervals and Δratios were drawn with Microsoft Excel and labeled as the RR graph and the Δratio graph, respectively. The heart rate (HR) was calculated as the mean of RR intervals for a period of 30 sec. The root-mean-square of Δratio for 30 sec was calculated, and defined as rMSΔ. The percentage of Δratio, which is more than 0.02 for 30 sec, was calculated, and defined as %Δ0.02. The difference between the maximum RR interval and minimum RR interval for 30 sec was calculated, and defined as RR dispersion.

The statistical comparison of background factors between the trimetaphan group and the nitroprusside group was done using Fisher's exact test for biometrical data (sex), and the unpaired t-test for continuous data (demographic data, operation time, blood loss volume, and duration of vasodilator administration). First, a statistical comparison of MAP, HR, rMSΔ, %Δ0.02, and RR dispersion was made among the trimetaphan group and the nitroprusside group at T1, T2, and T3. Initially, a comparison was made using the Friedman test as non-parametric method of ANOVA (analysis of variance) for related multiple groups, followed by the Kruskal-Wallis test with adjusted Bonferroni corrections. The significance was set at a p value of 0.05 or less. Next, a comparison of MAP, HR, rMSΔ, %Δ0.02, and RR dispersion between the combination of trimetaphan group and the nitroprusside group (group T-NP, n=20) and the nitroglycerin group (groupNG, n=5) was made at T0 and T1. The Wilcoxon signed rank test was used as non-parametric method for related two groups. The difference was considered significant at a p value of 0.05 or less. Data are presented as the mean±SEM.

RESULTS

The clinical characteristics and procedural summary are listed in Table 1. There was no significant difference in age, sex, weight, duration of vasodilator, and intraoperative blood loss volume between the group T and the group NP. The typical RR graph and Δratio graph of each group are shown in Figure 1 and Figure 2.

At first, comparison with the group T and group NP was made at T1, T2, and T3. There was no significant difference in HR, MAP, rMSΔ, %Δ0.02, and RR dispersion at T1. The MAP did not change from T1 to

Table 1. Demographic characteristics and peri-operative data

	Trimetaphan (n=10)	Nitroprusside (n=10)	Nitroglycerin (n=5)
Age; years	43.5±9.1	51.3±16.0	64±8.1
Sex; F/M	10/0	7/3	5/0
Weight (kg)	51.6±6.3	56.7±7.4	52±3.2
Operation			
Mastectomy / Mastectomy & Mammoplasty	7/3	8/0	3/0
ENT		2	
Plastic Surgery			1
Laparocholecystectomy			1
Orthopediaytric surgery			
Hypertension	0	0	4
Ischemic heart disease	0	0	1
>65 years old	0	1	4
Estimated blood loss (ml)	147±196	102±74	145±175
Maintenance Infusion rate of the hypotensive agent (μg/kg/min)	33±19	10±19	1.4±0.5
Cumulative dose of the hypotensive agent (mg)	122±134	5.4±5.4	10±10
Duration of vasodilator administration (min)	90±101	84±100	105±68

F, female; M, male Mean±SD, or number.

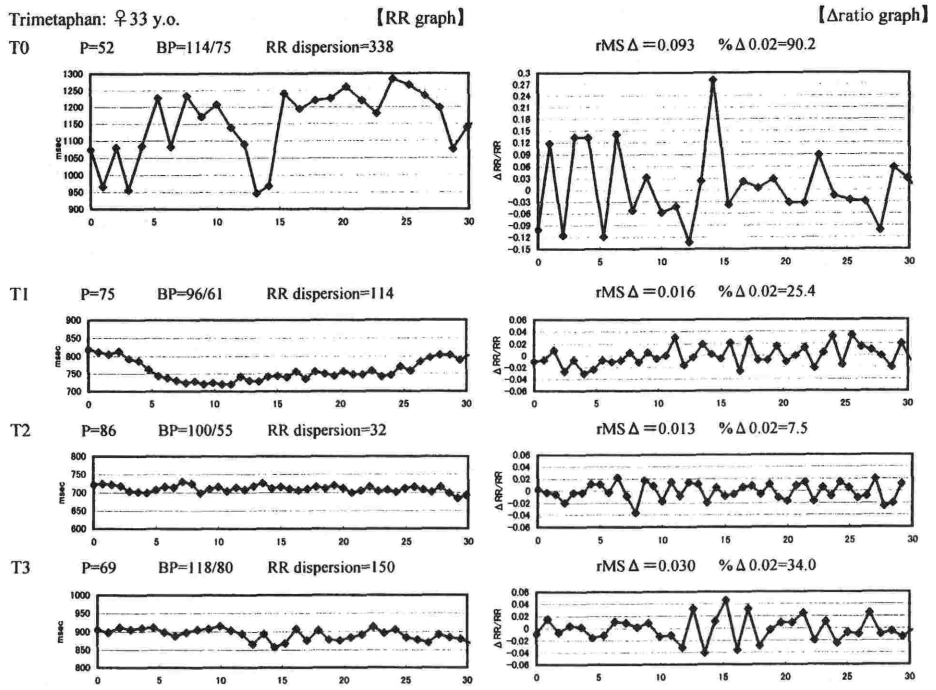

Figure 1. RR graph and Δ ratio graph of a Trimetaphan case

T0: Before Anesthesia, T1: Before Skin Incision, T2: Hypotension (20min), T3: After Hypotension (20min)

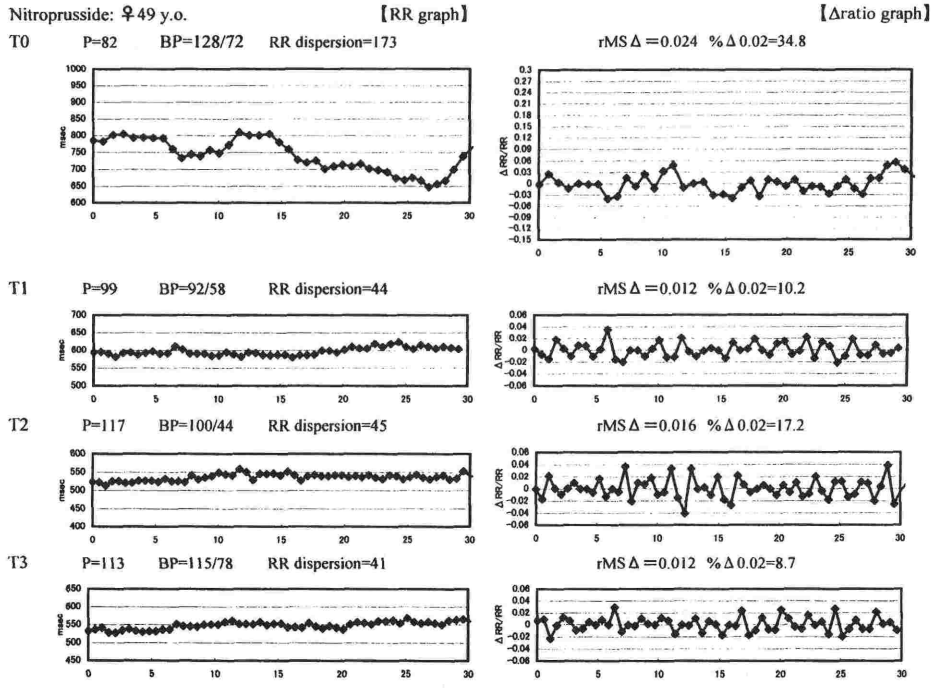

Figure 2. RR graph and Δ ratio graph of a Nitroprusside case

T0: Before Anesthesia, T1: Before Skin Incision, T2: Hypotension (20min), T3: After Hypotension (20min)

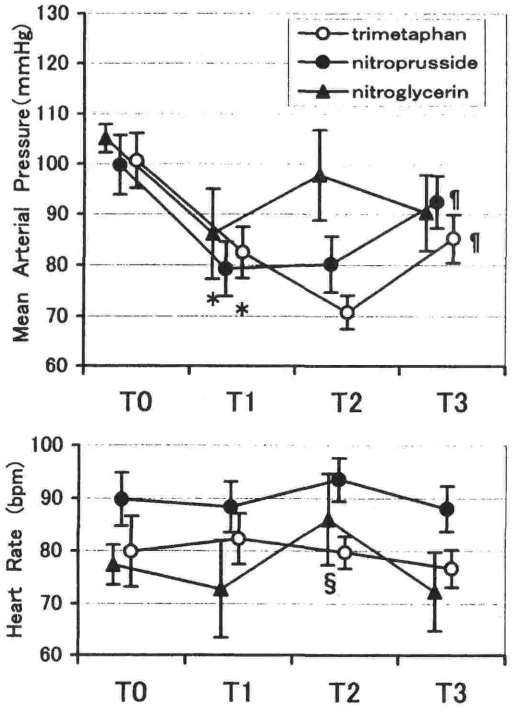

Figure 3. MAP and HR change after administration of trimetaphan, nitroprusside, and nitroglycerin
*p<0.05 vs T0 (group NG and group T-NP) § p<0.05 vs T1. ¶p<0.05 vs T2. Error bar denote SEM. T0: Before Anesthesia, T1: Before Skin Incision, T2: Hypotension (20min), T4: After Hypotension (20-min)

T2 in the group T and the group NP significantly, but increased from T2 to T3 in the both groups significantly. There was no significant difference in MAP between the two groups at T1, T2, and T3. The HR did not change in the group T and the group NP at T1, T2, and T3. Administration of trimetaphan led to a significant decrease in RR dispersion, rMSΔ, and %Δ0.02 at T2 ($p<0.05$, vs. T1), but did not cause zero value of RR dispersion and rMSΔ. Discontinuation of trimetaphan led to a significant increase in rMSΔ and %Δ0.02 at T3 ($p<0.05$, vs. T2). At T2, RR dispersion, rMSΔ, and %Δ0.02 of the group T were significantly lower than those of the group NP. There was no significant change in RR dispersion, rMSΔ, and %Δ0.02 at T1, T2, and T3 in the group NP.

Finally, a comparison of the group NG and the group T-NP were made before and after induction of anesthesia. The RR dispersion decreased from T0 to T1 in the group T-NP. However, no remarkable changes in RR dispersion, rMSΔ, and %Δ0.02 was observed in the group NG, and those parameters kept low values from T0 to T1.

DISCUSSION

The first issue of this study is whether or not an

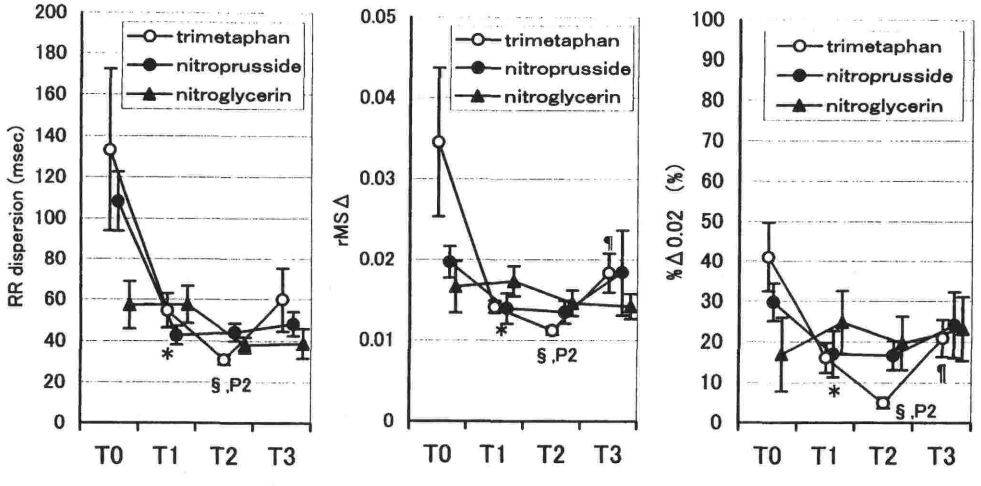

Figure 4. RR dispersion, rMSΔ, and %Δ0.02 after administration of trimetaphan, nitroprusside, and nitroglycerin
*p<0.05 vs T0 (group T-NP) § p<0.05 vs T1. ¶p<0.05 vs T2. P2 p<0.05 trimetaphan vs nitroprusside Error bar denote SEM. T0: Before Anesthesia, T1: Before Skin Incision, T2: Hypotension (20min), T3: After Hypotension (20min)

adequate dose of each vasodilator was administered. In the group T and the group NP, MAP did not change significantly at T1 and T2, before induced hypotension and at 20 min after administration of each vasodilator; and MAP was elevated by the discontinuation of the vasodilators. In the group NP, HR increased slightly at T2, but the change was not statistically significant. Usually MAP decline after the induction of anesthesia followed by the maintenance dose of GOS, if no nociceptive stimulation is added. Therefore, it is thought that an adequate amount of each vasodilator was administrated to offset a rise in MAP caused by the nociceptive stimulation after skin incision in the group T and the group NP.

The next question is whether trimetaphan made any significant changes on the RR graph in contrast with nitroprusside. Looking over the entire RR graph, there are small waves that constitute 3 to 6 heartbeats, a 2.5 to 6 seconds cycle, and larger waves that constitute a 7 to 30 seconds cycle (Figure 5). In the normal sinus rhythm, amplitudes of small waves, RR interval fluctuations by each beat, are limited within a narrow range. Larger waves, or noticeable changes in the RR intervals or heart rate arise from the overlap of small RR interval fluctuations. So, in general, the amplitude of small waves is limited within a relatively narrow range. In contrast to the small waves, the larger waves sometimes disappear (constant heart rate), or have large amplitude (rapid heart rate decrease or increase). To examine the amplitude of the small waves, not the value of the RR interval but the ΔRR, the difference of two consecutive RR intervals, is useful. This time the chronological plot of ΔRR /RR (Δratio graph) was adopted instead of the ΔRR. Visually, there are little difference between the chronological plot of ΔRR and Δratio. However, the ΔRR is determined by autonomic activity and certain factors (ion channels, extra/intra cellar ion concentrations, and etc.) that predominate in the RR interval. Therefore, since it is inferred that the Δratio is more representative of the electric state of the pacemaker cells, we adopted the Δ ratio graph to examine the small wave. The parameters are different for amplitude of the RR graph and the Δ ratio graph. Small waves have much smaller amplitude

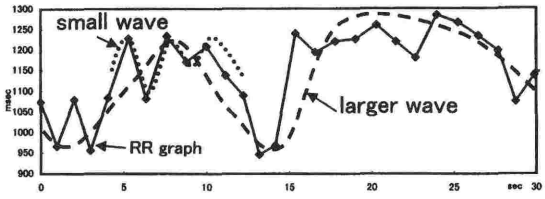

Figure 5. Small wave and larger wave on RR graph

than the larger waves and are sometimes affected by the larger waves. So the standard deviation (rMSΔ) or the percentage of the Δratio, which is bigger than a threshold for 30 seconds, is more representative of the amplitude of the Δratio graph than the difference between the maximum value and the minimum value for 30 seconds. In this study the threshold of Δratio was set at 0.02, because the administration of trimetaphan caused Δratio to be less than 0.02 in almost all cases, so that it is an arbitrary value. On the other hand, the larger waves have 7 to 30 seconds cycle, and the amplitude is sometimes much bigger than the small waves, so the RR dispersion, the simple difference between the maximum value and the minimum value can be sufficiently representative of the amplitude of the larger waves. A power spectrum analysis of HRV has revealed that the power of high frequency spectrum (HF: 0.15-0.4 Hz, 2.5-6.7 second cycle) correlates to parasympathetic nervous activity, and that the power of the low frequency spectrum (LF: 0.04-0.15 Hz, 6.7-25 second cycle) or LF/HF ratio correlates to sympathetic nervous activity. Therefore, from the coincidence of the frequency, it is inferred that the amplitude of the small waves in the RR graph or the Δratio graph corresponds to HF power and the amplitude of the larger waves in the RR graph corresponds to LF power approximately. This evidence supports the speculation that small waves in the RR graph or the Δratio graph corresponds to parasympathetic nervous activity, and the larger waves in the RR graph correspond to sympathetic nervous activity when the morphology of the RR graph and the Δratio graph is examined in a range from 30 seconds to minutes. This speculation leads to the hypothesis that blocking of autonomic ganglia with trimetaphan reduces the amplitude of the RR graph and the Δratio

graph. The results of this study support this hypothesis.

The third consideration is whether GOS anesthesia reduces the amplitude of the RR graph and the Δ ratio graph. In group T and group NP, the amplitude of the RR graph decreased after the induction of anesthesia, and the decrease lasted during anesthesia in spite of nociceptive stimulation. This result may represent the phenomena of "cardiovascular stability with anesthesia". But it is imprudent to conclude that GOS anesthesia always reduces the amplitude of the RR graph from the results of this study. In group NG, the amplitude of the RR graph did not change by the induction of anesthesia significantly. This fact shows that some limitations as complicating disease or medication exist to adopt RR graph as real time monitoring of autonomic activity and cardiac function during anesthesia. Anyway further investigations with sympathetic/parasympathetic agonist/antagonist will be needed to examine the usefulness of RR graph and Δ ratio graph during anesthesia.

The fourth consideration is whether HRV arises from only autonomic nervous activity. At T2 in group T, the larger wave of the RR graph diminished almost completely, while the small waves still remained. The amplitude of the Δ ratio graph was reduced but not completely; and it maintained the same irregular saw tooth structure as before administration, which is reminiscent of chaos. Some explanations for this are that the dose of trimetaphan may be insufficient to block autonomic ganglion completely; or the ganglion blocking effect by trimetaphan may be weaker in the parasympathetic nerve than in the sympathetic nerve. However, on the analogy of a morphological change in the RR graph and the Δ ratio graph another speculation follows: it is possible that the small waves which were thought to be caused by the parasympathetic nerve are essentially generated from another system, for example the sinus node itself, and the parasympathetic nerve plays only incremental part in the amplitude of small waves. Considering that the overall phenomena of life itself is chaotic[4], and systems are well synchronized most of the time, breaking down the least when every different system is chaotic, the latter possibility that —both the electrical activity of the sinus node and the cardiac parasympathetic nerve possess a chaotic rhythm— seems a reasonable explanation.

CONCLUSION

Trimetaphan administration under GOS anesthesia reduces the amplitude of RR graph and Δ ratio graph.

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